

## CHAPTER 10

### GASTROINTESTINAL ASSESSMENT

#### INTRODUCTION

##### Background

In contrast to the wealth of research data available in animal models, there is relatively little information on the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the human digestive system. Though the pharmacokinetics of orally ingested TCDD in a human volunteer have been studied and reported (1), the pathologic lesions that have been studied in animals—gastric metaplasia with ulceration and ileitis, for example—have not been described in human populations where the principal route of exposure has been transcutaneous. Further, in two recent reports of extreme phenoxyherbicide toxicity by ingestion in three humans, the primary target organs were the central nervous system with associated coma and the musculoskeletal system with rhabdomyolysis and renal failure (2, 3).

The digestive system and, more specifically, the liver have been studied extensively and clearly defined as target organs for TCDD toxicity in numerous laboratory and domestic animals (4-8). Absorbed by the intestinal lymphatics and transported in the enterohepatic circulation by chylomicrons, TCDD ingested by rats (9-12) and guinea pigs (13) is preferentially stored in the liver. Hepatotoxic manifestations, which appear to be dose- and time-dependent, include cellular hypertrophy, parenchymal necrosis (principally centrilobular), and fatty degeneration (14-17). Much of the basic animal research into the mechanism of TCDD-induced hepatotoxicity has focused on the definition and function of the aryl hydroxylase (Ah) receptor, a stereospecific protein that is present in the cytosol of hepatic parenchymal cells (18-24). Capable of binding aromatic hydrocarbons, the species- and strain-specific Ah receptor mediates a broad range of biochemical/enzymatic reactions, many of which are dependent on the ferrocyclochrome P-450 enzyme system (18, 25, 26).

A host of hepatic biochemical reactions have been studied related to TCDD toxicity including enhanced lipid peroxidation (27, 28, 29), hepatic prostaglandin synthetase activity (30), and inhibition of glutathione peroxidase (29). Results from several lines of biochemical investigation have created a bridge between animal and human studies including research into lipid (31-34) and porphyrin (35-39) metabolism. In rats, TCDD has been shown to increase the activity of glucuronyl transferase (40) which, in turn, has led to the use of urinary d-glucaric acid as a marker for TCDD exposure in this and other human epidemiologic studies (41, 42, 43).

Numerous human morbidity studies from the industrial sector have noted abnormal indices of liver function that in most cases were not associated with any other clinical evidence for liver or gastrointestinal disease (44-48). Further, in longer-term followup studies, abnormalities noted at the time of acute exposure appeared to resolve over time (49-53). A recent report, based on a more accurate estimate of prior TCDD exposure employing adipose tissue levels, found no abnormalities in standard liver function tests related to the body burden of dioxin (54).

In summary, basic research has provided valuable insight into the biochemical and molecular basis for TCDD toxicity in many mammalian species. But to date, clinical endpoints in the gastrointestinal system related to dioxin exposure in humans have been transient and not associated with any long-term sequelae.

More detailed summaries of the pertinent scientific literature for the gastrointestinal assessment can be found in the report of the previous analyses of the 1987 examination data (55).

### **Summary of Previous Analyses of the 1987 Examination Data**

Overall, the gastrointestinal assessment did not find the health of the Ranch Hand group to be significantly different from the Comparison group. Group differences based on verified historical data from the questionnaire were not significant for eight categories of liver disease. No significant group difference was found for past or present occurrence of peptic ulcers. The prevalence of hepatomegaly diagnosed at the physical examination also was not significantly different between groups. The only significant finding from the laboratory examination variables was that the Ranch Hands had a higher mean alkaline phosphatase than the Comparisons. This also was noted at the 1985 examination. Group differences for the other laboratory variables (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], total bilirubin, direct bilirubin, lactic dehydrogenase [LDH], cholesterol, high-density lipoprotein [HDL], cholesterol-HDL ratio, triglycerides, and creatine kinase) were not significant. Stratified analyses to explore group-by-covariate interactions did not disclose any consistent pattern of significant group differences within any subgroup. The exposure index data often exhibited positive dose-response relationships, but results of the statistical analyses generally were not significant. The longitudinal analyses of AST, ALT, and GGT showed that the group differences did not change significantly between the Baseline examination and the 1987 examination.

### **Parameters of the Gastrointestinal Assessment**

#### ***Dependent Variables***

Questionnaire, physical examination, and laboratory data were used in the gastrointestinal assessment. The questionnaire data were organized by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) medical coding categories.

#### **Questionnaire Data**

During the health interview in 1987, each study participant was asked about the occurrence of hepatitis, jaundice, cirrhosis, enlarged liver, and other liver conditions. This self-reported information was combined with information from the Baseline and 1985 examinations and verified by medical record review. The verified results were then grouped into eight categories of disorders for analysis: viral hepatitis, acute and subacute necrosis of the liver, chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related cirrhosis were analyzed separately), liver abscess and sequelae of chronic liver disease, other disorders of the liver (ICD codes 5730-5739, 7901, 7904, 7905, and 7948), jaundice (unspecified, not of the newborn), and hepatomegaly. Viral hepatitis was verified by serological testing. The abnormalities in the "other disorders" category were primarily

abnormal liver scans and unspecified disorders of the liver. Abnormal enzyme elevations and unspecified hepatitis (8 Ranch Hands, 13 Comparisons) also fell in this category. No analyses were done for acute and subacute necrosis of the liver or for liver abscess and sequelae of chronic liver disease because no Ranch Hands had these conditions. Two Comparisons had necrosis of the liver after service in Southeast Asia (SEA) and one had an abscess of the liver.

Information on the occurrence of skin bruises, patches, and sensitivity also was captured in the questionnaire. This self-reported information was combined with information from the Baseline and 1985 examinations, verified, and analyzed as part of the gastrointestinal assessment. This variable is considered a surrogate measure for a possible symptom of porphyria cutanea tarda. A verified ulcer variable based on gastric, duodenal, peptic, and gastrojejunal ulcers also was analyzed.

For each condition, participants with a pre-SEA diagnosis were excluded from the analysis.

#### **Physical Examination Data**

One variable from the 1987 physical examination, current hepatomegaly, was analyzed in the gastrointestinal assessment. This variable was coded as yes/no. Participants whose blood contained hepatitis B surface antigen (HB<sub>s</sub>Ag) were excluded from the analysis of current hepatomegaly.

#### **Laboratory Examination Data**

The 1987 examination emphasized evaluation of laboratory data, particularly for the hepatic function. Thirteen laboratory variables were analyzed: AST (U/L), ALT (U/L), GGT (U/L), alkaline phosphatase (U/L), d-glucaric acid ( $\mu$ M), total bilirubin (mg/dl), direct bilirubin (mg/dl), LDH (U/L), cholesterol (mg/dl), high-density lipoproteins (HDL in mg/dl), cholesterol-HDL ratio, triglycerides (mg/dl), and creatine kinase (U/L). The analyses of d-glucaric acid were based on urine collected during the 1985 examination and stored at -70°C. Each laboratory variable was analyzed in both continuous and discrete forms. All were dichotomized as high versus normal for the discrete analyses except HDL, which was dichotomized as low versus normal. Table 10-1 shows the ranges used to determine normal/abnormal cutpoints. A natural logarithm transformation was applied to all the variables except d-glucaric acid, which was analyzed on the square root scale. For direct bilirubin, the transformation was done after adding 0.1 to each value because several participants had levels of 0.0 mg/dl.

Participants whose blood contained HB<sub>s</sub>Ag and participants with body temperature greater than or equal to 100°F were excluded from the analysis of the laboratory variables. For d-glucaric acid, these exclusionary criteria were determined from the 1985 examination data.

#### **Covariates**

The gastrointestinal assessment examined the effects of covariates in the adjusted statistical analyses. Blood type was a candidate covariate for the adjusted analysis of verified ulcer. Age, race, current alcohol use, lifetime alcohol history, lifetime industrial

**TABLE 10-1.**

**Statistical Analysis for the Gastrointestinal Assessment**

**Dependent Variables**

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Viral Hepatitis	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC, OCC	U:LR A:LR
Acute and Subacute Necrosis of the Liver	Q/PE-V	D	Yes No	--	--
Chronic Liver Disease and Cirrhosis (Alcohol-Related)	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
Chronic Liver Disease and Cirrhosis (Nonalcohol- Related)	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, CS, FT A:LR
Liver Abscess and Sequelae of Chronic Liver Disease	Q/PE-V	D	Yes No	--	--
Other Disorders of the Liver	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
Jaundice (Unspecified)	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, CS, FT A:LR
Hepatomegaly	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
Verified Ulcer	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC, BLOOD	U:LR A:LR
Skin Bruises, Patches, or Sensitivity	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR

**TABLE 10-1. (Continued)**

**Statistical Analysis for the Gastrointestinal Assessment**

**Dependent Variables**

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Current Hepatomegaly	PE	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
AST (U/L)	LAB	D/C	High: $\geq 48$ Normal: $\leq 47$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM L:GLM
ALT (U/L)	LAB	D/C	High: $\geq 37$ Normal: $\leq 36$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM L:GLM
GGT (U/L)	LAB	D/C	High: $\geq 86$ Normal: $\leq 85$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM L:GLM
Alkaline Phosphatase (U/L)	LAB	D/C	High: $\geq 137$ Normal: $\leq 136$	AGE, RACE, WINE, LWINE, IC, DC	U:LR, GLM, CS, FT A:LR, GLM
D-Glucaric Acid ( $\mu\text{M}$ )	LAB	D/C	High: $\geq 99$ Normal: $\leq 98$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM, CS, FT A:LR, GLM
Total Bilirubin (mg/dl)	LAB	D/C	High: $\geq 1.5$ Normal: $< 1.5$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
Direct Bilirubin (mg/dl)	LAB	D/C	High: $\geq 0.41$ Normal: $\leq 0.40$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
LDH (U/L)	LAB	D/C	High: $\geq 191$ Normal: $\leq 190$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM, CS, FT A:LR, GLM
Cholesterol (mg/dl)	LAB	D/C	High: $\geq 261$ Normal: $\leq 260$	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM

**TABLE 10-1. (Continued)**

**Statistical Analysis for the Gastrointestinal Assessment**

**Dependent Variables**

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
HDL (mg/dl)	LAB	D/C	Low: <30 Normal: ≥30	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
Cholesterol-HDL Ratio	LAB	D/C	High: >5 Normal: ≤5	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
Triglycerides (mg/dl)	LAB	D/C	High: ≥321 Normal: ≤320	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
Creatine Kinase (U/L)	LAB	D/C	High: ≥233 Normal: ≤232	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM

**Covariates**

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Blood (BLOOD)	MIL	D	A B AB O
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew

**TABLE 10-1. (Continued)****Statistical Analysis for the Gastrointestinal Assessment****Covariates**

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Current Alcohol Use (ALC) (drinks/day)	Q-SR	D/C	0-1 >1-4 >4
Lifetime Alcohol History (DRKYR) (drink- years)	Q-SR	D/C	0 >0-40 >40
Current Wine Use (WINE) (drinks of wine/day)	Q-SR	D/C	0 >0
Lifetime Wine History (LWINE) (wine- years)	Q-SR	D/C	0 >0
Industrial Chemical Exposure (IC)	Q-SR	D	Yes No
Degreasing Chemical Exposure (DC)	Q-SR	D	Yes No

**Abbreviations**

Data Source: LAB--1987 SCRF laboratory results  
MIL--Air Force military records  
PE--1987 SCRF physical examination  
Q/PE-V--1987 questionnaire and physical examination (verified)  
Q-SR--1987 questionnaire (self-reported) [1985 questionnaire when used  
with d-glucaric acid]

Data Form: D--Discrete analysis only  
D/C--Discrete and continuous analyses for dependent variables; appropriate  
form for analysis (either discrete or continuous) for covariates

Statistical Analyses: U--Unadjusted analyses  
A--Adjusted analyses  
L--Longitudinal analyses

Statistical Methods: GLM--General linear models analysis  
LR--Logistic regression analysis  
CS--Chi-square contingency table test  
FT--Fisher's exact test

chemical exposure, and lifetime degreasing chemical exposure were candidate covariates for the adjusted analyses of all of the laboratory variables except alkaline phosphatase. For alkaline phosphatase, current wine consumption was used instead of current alcohol use, and lifetime wine history was used instead of lifetime alcohol history since wine consumption showed a strong negative association with alkaline phosphatase in the 1985 examination. Because of a strong association, occupation was used as a covariate for the hepatitis analyses.

The lifetime alcohol history and current alcohol use covariates were based on self-reported information from the questionnaire. For lifetime alcohol history, the respondent's average daily alcohol consumption was determined for various drinking stages throughout his lifetime, and an estimate of the corresponding total number of drink-years (1 drink-year is the equivalent of drinking 1.5 ounces of 80-proof alcoholic beverage per day for 1 year) was derived. The current alcohol use covariate was based on the average drinks per day for the month prior to completing the questionnaire.

Age, current alcohol use, and lifetime alcohol history were treated as continuous variables for all adjusted analyses and were categorized to explore interactions, which are presented in Appendix Table I-1. Current wine use and lifetime wine history were treated as continuous variables for the adjusted alkaline phosphatase analyses, and were similarly categorized for interaction exploration. Degreasing chemical exposure and industrial chemical exposure were categorized for all analyses. The cutpoints used for categorization are specified in Table 10-1. In discussing the alcohol-related covariates, the terms light, moderate, and heavy are sometimes used to describe the current drinking habits of the participants; for lifetime alcohol use, never replaces light. These distinctions correspond to the three drinking categories in Table 10-1 for current alcohol use and lifetime alcohol history.

#### ***Relation to Baseline, 1985, and 1987 Studies***

The verified questionnaire data analyzed in the 1987 assessment were organized by ICD-9-CM medical coding categories. Ulcers were not analyzed in the Baseline report.

For the laboratory variables, the gastrointestinal assessment was expanded to include HDL, cholesterol-HDL ratio, and creatine kinase subsequent to the Baseline study. The statistical analysis of d-glucaric acid was added for the previous report and is based on data collected at the 1985 physical examination. All other laboratory variables analyzed in the 1987 examination were analyzed in the Baseline and 1985 studies.

The longitudinal assessment analyzed AST, ALT, and GGT.

#### **Statistical Methods**

The basic statistical analysis methods used in the gastrointestinal assessment are described in Chapter 4, Statistical Methods. The modeling strategy was modified for the adjusted analyses of the questionnaire and physical examination variables. For these variables, the stepwise model examined the covariate main effects only; it did not include pairwise covariate interactions or dioxin-by-covariate interactions. Also, the adjusted analyses for these variables always kept age in the final model, regardless of the significance level.



Table 10-1 summarizes the statistical analyses performed for the 1987 gastrointestinal assessment. The first part of this table identifies the dependent variables, source of the data, form(s) of the data, cutpoints, candidate covariates, and statistical methods. The second part of the table provides additional information on the candidate covariates. Abbreviations are used extensively in the body of the table and are defined in footnotes. Dependent variable and covariate data were missing for some participants. Table 10-2 summarizes the number of participants with missing data and the number who were excluded from analyses for medical reasons.

Three statistical models were used to examine the association between a dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour of duty in SEA. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under the minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (55). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

Appendix I-1 contains graphic displays of individual dependent variables versus initial dioxin for the minimal and maximal cohorts, and individual variables versus current dioxin for Ranch Hands and Comparisons. Appendix I-2 presents graphics for dioxin-by-covariate interactions as determined by various statistical models. A guide to assist in interpreting the graphics is found in Chapter 4.

## RESULTS

### Exposure Analysis

#### *Questionnaire Variables*

##### **Viral Hepatitis**

Preliminary screening analyses found that the incidence of hepatitis differed significantly among occupational categories ( $p < 0.001$ ). Enlisted flyers and enlisted groundcrew had a higher incidence than officers. This finding was independent of group membership. For Ranch Hands in the maximal cohort, 53.9 percent of enlisted flyers and 42.4 percent of enlisted groundcrew had a history of hepatitis in contrast to 28.6 percent for officers. The relative frequencies for Comparisons with background levels of dioxin ( $\leq 10$  ppt) were 52.9, 46.5, and 29.6 percent for the enlisted flyers, enlisted groundcrew, and officer occupational categories. Because occupation also is associated highly with both current and initial levels of dioxin (enlisted groundcrew have the highest dioxin levels followed by enlisted flyers and officers, see Chapter 2, Dioxin Assay), an additional model that included occupation was examined in each analysis. Appendix Table I-2 presents the results of these analyses.

**TABLE 10-2.**  
**Number of Participants Excluded and With Missing Data for the**  
**Gastrointestinal Assessment**

Variable	Variable Use	Assumption (Ranch Hands Only)		Categorized Current Dioxin	
		Minimal	Maximal	Ranch Hand	Comparison
D-Glucaric Acid (1985)	DEP	15	25	25	36
Current Alcohol Use	COV	3	5	5	0
Current Alcohol Use (1985)	COV	17	26	25	35
Current Wine Use	COV	4	5	5	1
Lifetime Alcohol History	COV	6	9	9	2
Lifetime Alcohol History (1985)	COV	35	51	52	53
Lifetime Wine History	COV	4	6	6	2
Blood Type	COV	2	4	5	2
Pre-SEA Viral Hepatitis	EXC	15	22	21	25
Pre-SEA Acute and Subacute Necrosis of the Liver	EXC	0	0	0	1
Pre-SEA Chronic Liver Disease and Cirrhosis (Alcohol-Related)	EXC	1	1	1	3
Pre-SEA Other Disorders of the Liver	EXC	1	4	3	9
Pre-SEA Jaundice	EXC	14	21	19	24
Pre-SEA Hepatomegaly	EXC	1	1	1	1
Pre-SEA Ulcer	EXC	7	18	19	22
Pre-SEA Skin Bruises, Patches, or Sensitivity	EXC	11	18	15	18
Positive HB <sub>s</sub> Ag	EXC	3	4	7	4
Temperature $\geq 100$ at 1987 Laboratory Exam	EXC	1	1	1	3
Positive HB <sub>s</sub> Ag (1985)	EXC	1	1	2	3
Temperature $\geq 100$ at 1985 Laboratory Exam	EXC	2	2	1	1

DEP--Dependent variable (missing data).

COV--Covariate (missing data).

EXC--Exclusion.

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analysis did not find a significant association with hepatitis under the minimal assumption (Table 10-3 [a]:  $p=0.613$ ), but the association was marginally significant under the maximal assumption (Table 10-3 [b]: Est. RR=1.11,  $p=0.051$ ). The incidences of hepatitis were 32.8, 42.0, and 42.8 percent for the low, medium, and high initial dioxin categories of the maximal cohort. Adjusting for age and race, the relative risk of hepatitis was significantly more than 1 under both assumptions (Table 10-3 [c]: Adj. RR=1.19,  $p=0.028$  for the minimal cohort; Table 10-3 [d]: Adj. RR=1.24,  $p<0.001$  for the maximal cohort). However, the relative risk became nonsignificant after adding occupation to the model (Appendix Table I-2:  $p=0.912$  under the minimal assumption and  $p=0.777$  under the maximal assumption).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the association between current dioxin and hepatitis did not differ significantly between time since tour strata based on the unadjusted analyses (Table 10-3 [e] and [f]:  $p=0.588$  and  $p=0.296$ , respectively). After adjustment for age and race, the current dioxin-by-time interaction remained nonsignificant for both assumptions (Table 10-3 [g] and [h]:  $p=0.370$  and  $p=0.224$ ), although the adjusted relative risk was significant for Ranch Hands with a later tour (time $\leq$ 18.6: Adj. RR=1.30,  $p=0.046$  for the minimal assumption; Adj. RR=1.33,  $p=0.002$  for the maximal assumption). The percentages of these Ranch Hands with hepatitis in the low, medium, and high current dioxin categories were 34.7, 41.1, and 34.6 percent under the minimal assumption, and 27.6, 36.9, and 40.7 percent under the maximal assumption. Adjusting for age and race, the relative risk was of borderline significance under the maximal assumption for Ranch Hands with an early tour (time $>$ 18.6: Adj. RR=1.15,  $p=0.080$ ). However, these findings became nonsignificant when occupation was included in the model.

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted analysis of categorized current dioxin did not find an overall difference in the incidence of hepatitis among the four current dioxin categories (Table 10-3 [i]: 41.5%, 35.5%, 41.4%, and 44.2% for the background, unknown, low, and high current dioxin categories,  $p=0.179$ ), although the relative risk for the unknown versus background contrast was marginally less than 1 (Est. RR=0.78, 95% C.I.: [0.59,1.01],  $p=0.062$ ).

After adjusting for age, race, and industrial chemical exposure, the overall current dioxin effect became significant (Table 10-3 [j]:  $p=0.022$ ). The relative risk for the unknown versus background contrast remained marginally less than 1 (Adj. RR=0.77, 95% C.I.: [0.58,1.01],  $p=0.061$ ), while the adjusted relative risk for the high versus background contrast became significantly more than 1 (Adj. RR=1.42, 95% C.I.: [1.01,2.00],  $p=0.047$ ). However, all contrasts became nonsignificant after including occupation in the model (Appendix Table I-2:  $p>0.25$  for each contrast). Adjusting for age, race, and occupation, the relative risk for the high versus background contrast was reduced to 1.03 (95% C.I.: [0.72,1.47],  $p=0.859$ ).

**TABLE 10-3.**  
**Analysis of Viral Hepatitis**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=506)	Low	126	36.5	1.04 (0.90,1.20)	0.613
	Medium	252	44.8		
	High	128	42.2		
b) Maximal (n=720)	Low	183	32.8	1.11 (1.00,1.24)	0.051
	Medium	357	42.0		
	High	180	42.8		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=506)	1.19 (1.02,1.40)	0.028	AGE (p<0.001) RACE (p=0.011)
d) Maximal (n=720)	1.24 (1.10,1.39)	<0.001	AGE (p<0.001) RACE (p=0.003)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-3. (Continued)

## Analysis of Viral Hepatitis

Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=506)	≤18.6	34.7 (72)	41.1 (124)	34.6 (52)	1.04 (0.82,1.33)	0.588 <sup>b</sup> 0.722 <sup>c</sup>
	>18.6	46.3 (54)	47.3 (129)	44.0 (75)	0.96 (0.79,1.16)	0.672 <sup>c</sup>
f) Maximal (n=720)	≤18.6	27.6 (105)	36.9 (187)	40.7 (81)	1.14 (0.96,1.35)	0.296 <sup>b</sup> 0.131 <sup>c</sup>
	>18.6	44.6 (74)	43.9 (173)	47.0 (100)	1.01 (0.87,1.17)	0.879 <sup>c</sup>

Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=506)	≤18.6	1.30 (1.00,1.68)	0.370 <sup>b</sup> 0.046 <sup>c</sup>	AGE (p<0.001) RACE (p=0.011)
	>18.6	1.12 (0.91,1.38)	0.267 <sup>c</sup>	
h) Maximal (n=720)	≤18.6	1.33 (1.11,1.60)	0.224 <sup>b</sup> 0.002 <sup>c</sup>	AGE (p<0.001) RACE (p=0.002)
	>18.6	1.15 (0.98,1.35)	0.080 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.  
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-3. (Continued)**

**Analysis of Viral Hepatitis**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	761	41.5	All Categories		0.179
Unknown	335	35.5	Unknown vs. Background	0.78 (0.59,1.01)	0.062
Low	191	41.4	Low vs. Background	0.99 (0.72,1.37)	0.967
High	181	44.2	High vs. Background	1.12 (0.80,1.55)	0.512
Total	1,468				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	761	All Categories		0.022	AGE (p<0.001) RACE (p<0.001) IC (p=0.006)
Unknown	335	Unknown vs. Background	0.77 (0.58,1.01)	0.061	
Low	191	Low vs. Background	0.99 (0.71,1.38)	0.935	
High	181	High vs. Background	1.42 (1.01,2.00)	0.047	
Total	1,468				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
 High (Ranch Hands): Current Dioxin >33.3 ppt.

## **Chronic Liver Disease and Cirrhosis (Alcohol-Related)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The relative risk was less than 1, but not significant, for both the unadjusted and adjusted analyses of alcohol-related chronic liver disease and cirrhosis (Table 10-4 [a-d]:  $p > 0.15$  for each analysis under both the minimal and maximal assumptions).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The interaction between current dioxin and time since tour was not significant under both the minimal (Table 10-4 [e]:  $p = 0.317$ ) and maximal (Table 10-4 [f]:  $p = 0.463$ ) assumptions in the unadjusted analyses of alcohol-related chronic liver disease and cirrhosis. Under both assumptions, the current dioxin-by-time interaction remained nonsignificant after covariate adjustment (Table 10-4 [g] and [h]:  $p = 0.200$  and  $p = 0.199$  for the minimal and maximal assumptions), although the adjusted relative risk for Ranch Hands with an early tour was marginally less than 1 (time > 18.6: Adj. RR = 0.64,  $p = 0.082$  under the minimal assumption; Adj. RR = 0.72,  $p = 0.087$  under the maximal assumption).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of alcohol-related chronic liver disease did not differ significantly among the four current dioxin categories in either the unadjusted (Table 10-4 [i]:  $p = 0.475$ ) or adjusted (Table 10-4 [j]:  $p = 0.449$ ) analysis. None of the three Ranch Hand versus background contrasts was significant for either analysis ( $p > 0.20$  for each contrast).

## **Chronic Liver Disease and Cirrhosis (Nonalcohol-related)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, the initial dioxin analyses of nonalcohol-related chronic liver disease and cirrhosis were not significant (Table 10-5 [a-d]:  $p > 0.25$  for the unadjusted and adjusted analyses).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The current dioxin-by-time since tour interaction was not evaluated because only one Ranch Hand with an early tour had nonalcohol-related chronic liver disease. The association between current dioxin and nonalcohol-related chronic liver disease and cirrhosis was not significant for Ranch Hands with a later tour in both the unadjusted minimal (Table 10-5 [e]:  $p = 0.553$ ) and maximal (Table 10-5 [f]:  $p = 0.807$ ) analyses. No adjusted analyses were done due to sparse data.

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of nonalcohol-related chronic liver disease and cirrhosis did not differ significantly among current dioxin categories (Table 10-5 [g] and [h]: 0.9%, 0.9%, 1.5%, and 0.0% for the background, unknown, low, and high categories;  $p = 0.446$  and  $p = 0.226$  in the unadjusted and adjusted analyses).

TABLE 10-4.

## Analysis of Chronic Liver Disease and Cirrhosis (Alcohol-Related)

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=520)	Low	130	6.2	0.89 (0.62,1.29)	0.543
	Medium	259	2.7		
	High	131	6.1		
b) Maximal (n=741)	Low	185	4.9	0.91 (0.70,1.19)	0.488
	Medium	370	4.3		
	High	186	4.8		
Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
c) Minimal (n=514)	0.76 (0.51,1.13)		0.164	AGE (p=0.575) ALC (p<0.001) DRKYR (p=0.005)	
d) Maximal (n=732)	0.85 (0.64,1.12)		0.238	AGE (p=0.807) ALC (p<0.001) DRKYR (p=0.001)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.



TABLE 10-4. (Continued)

## Analysis of Chronic Liver Disease and Cirrhosis (Alcohol-Related)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=520)	≤18.6	5.6 (72)	1.6 (127)	5.6 (54)	1.10 (0.60,2.02)	0.317 <sup>b</sup> 0.747 <sup>c</sup>
	>18.6	8.6 (58)	3.8 (132)	5.2 (77)	0.74 (0.45,1.22)	0.236 <sup>c</sup>
f) Maximal (n=741)	≤18.6	4.7 (106)	2.6 (190)	4.8 (83)	1.01 (0.65,1.55)	0.463 <sup>b</sup> 0.977 <sup>c</sup>
	>18.6	6.3 (79)	5.6 (179)	4.8 (104)	0.82 (0.57,1.16)	0.259 <sup>c</sup>
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=514)	≤18.6	1.08 (0.57,2.06)		0.200 <sup>b</sup> 0.810 <sup>c</sup>	AGE (p=0.536) ALC (p<0.001)	
	>18.6	0.64 (0.39,1.06)		0.082 <sup>c</sup>	DRKYR (p=0.006)	
h) Maximal (n=732)	≤18.6	1.05 (0.67,1.64)		0.199 <sup>b</sup> 0.827 <sup>c</sup>	AGE (p=0.912) ALC (p<0.001)	
	>18.6	0.72 (0.50,1.05)		0.087 <sup>c</sup>	DRKYR (p=0.002)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-4. (Continued)

## Analysis of Chronic Liver Disease and Cirrhosis (Alcohol-Related)

## i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	3.3	All Categories		0.475
Unknown	345	4.6	Unknown vs. Background	1.42 (0.75,2.68)	0.286
Low	195	2.6	Low vs. Background	0.77 (0.29,2.02)	0.589
High	187	4.8	High vs. Background	1.47 (0.68,3.20)	0.330
Total	1,510				

## j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	781	All Categories		0.449	AGE (p=0.862) ALC (p<0.001)
Unknown	342	Unknown vs. Background	1.51 (0.77,2.96)	0.229	DRKYR (p=0.008)
Low	193	Low vs. Background	0.96 (0.36,2.58)	0.935	DC (p=0.076)
High	183	High vs. Background	1.72 (0.75,3.95)	0.202	
Total	1,499				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

**TABLE 10-5.**  
**Analysis of Chronic Liver Disease and Cirrhosis**  
**(Nonalcohol-Related)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=521)	Low	130	0.8	0.67 (0.24,1.86)	0.411
	Medium	260	1.2		
	High	131	0.0		
b) Maximal (n=742)	Low	185	0.5	0.88 (0.44,1.75)	0.711
	Medium	371	1.1		
	High	186	0.0		
Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
c) Minimal (n=521)	0.59 (0.21,1.69)		0.287	AGE (p=0.282)	
d) Maximal (n=742)	0.79 (0.40,1.56)		0.487	AGE (p=0.105)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-5. (Continued)**  
**Analysis of Chronic Liver Disease and Cirrhosis**  
**(Nonalcohol-Related)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	1.4 (72)	1.6 (128)	0.0 (54)	0.67 (0.18,2.48)	-- 0.553 <sup>b</sup>
	>18.6	0.0 (58)	0.8 (132)	0.0 (77)	--	--
f) Maximal (n=742)	≤18.6	0.9 (106)	1.6 (191)	0.0 (83)	0.90 (0.39,2.09)	-- 0.807 <sup>b</sup>
	>18.6	0.0 (79)	0.6 (179)	0.0 (104)	--	--

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

--: Relative risk/confidence interval/p-value not given due to the sparse number of abnormalities.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-5. (Continued)**  
**Analysis of Chronic Liver Disease and Cirrhosis**  
**(Nonalcohol-Related)**

**g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	0.9	All Categories		0.446
Unknown	345	0.9	Unknown vs. Background	0.98 (0.25,3.80)	0.999
Low	196	1.5	Low vs. Background	1.73 (0.44,6.74)	0.642
High	187	0.0	High vs. Background	--	0.446
Total	1,514				

**h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	786	All Categories		0.226	AGE (p=0.430)
Unknown	345	Unknown vs. Background	1.00 (0.26,3.91)	0.997	
Low	196	Low vs. Background	1.72 (0.44,6.72)	0.434	
High	187	High vs. Background	--	--	
Total	1,514				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

## **Other Disorders of the Liver**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under the minimal assumption, both the unadjusted and the adjusted initial dioxin analyses did not find a significant association with other disorders of the liver (Table 10-6 [a] and [c]:  $p=0.220$  and  $p=0.245$ , respectively). However, the relative risk was marginally significant under the maximal assumption (Table 10-6 [b] and [d]: Est. RR=1.19,  $p=0.051$  in the unadjusted analysis; Adj. RR=1.19,  $p=0.061$  in the adjusted analysis). The incidences were 5.0, 10.5, and 10.8 percent for the low, medium, and high initial dioxin categories of the maximal cohort.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the association between current dioxin and other disorders of the liver did not differ significantly between time since tour strata (Table 10-6 [e-h]:  $p>0.30$  for the unadjusted and adjusted analyses).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis found a marginally significant difference among the percentages of participants with "other disorders of the liver" (Table 10-6 [i]: 7.1%, 5.9%, 9.2%, and 11.8% for the background, unknown, low, and high current dioxin categories,  $p=0.087$ ). The high versus background relative risk was significantly more than 1 (Est. RR=1.75, 95% C.I.: [1.04,2.95],  $p=0.036$ ). The adjusted analysis showed similar results. After adjusting for age and current alcohol use, the overall contrast remained marginally significant (Table 10-6 [j]:  $p=0.084$ ) and the adjusted relative risk for the high versus background contrast remained significant (Adj. RR=1.78, 95% C.I.: [1.03,3.07],  $p=0.038$ ).

## **Jaundice**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Initial dioxin was not associated significantly with jaundice in either the unadjusted or adjusted analyses (Table 10-7 [a-d]:  $p>0.45$  for all minimal and maximal analyses).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Both the unadjusted and adjusted current dioxin and time since tour analyses for jaundice did not find a significant current dioxin-by-time interaction (Table 10-7 [e-h]:  $p>0.30$  for the minimal and maximal analyses).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted analysis of categorized current dioxin found a marginally significant difference among the incidences of jaundice (Table 10-7 [i]: 2.2%, 3.3%, 0.0%, and 1.1% for the background, unknown, low, and high current dioxin categories,  $p=0.056$ ) with significantly fewer cases in the low current dioxin category relative to the background category ( $p=0.042$ ). The overall contrast was significant in the adjusted analysis (Table 10-7 [j]:  $p=0.014$ ).

**TABLE 10-6.**  
**Analysis of Other Disorders of the Liver**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=520)	Low	129	9.3	1.15 (0.92,1.45)	0.220
	Medium	260	9.2		
	High	131	12.2		
b) Maximal (n=738)	Low	182	5.0	1.19 (1.00,1.41)	0.051
	Medium	370	10.5		
	High	186	10.8		
Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
c) Minimal (n=520)	1.15 (0.91,1.45)		0.245	AGE (p=0.907)	
d) Maximal (n=733)	1.19 (0.99,1.42)		0.061	AGE (p=0.794) ALC (p<0.001)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-6. (Continued)**  
**Analysis of Other Disorders of the Liver**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
<b>Assumption</b>	<b>Time (Yrs.)</b>	<b>Percent Yes/(n) Current Dioxin</b>			<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
		<b>Low</b>	<b>Medium</b>	<b>High</b>		
e) Minimal (n=520)						0.535 <sup>b</sup>
	≤18.6	4.2 (71)	8.6 (128)	9.3 (54)	1.22 (0.81,1.85)	0.338 <sup>c</sup>
	>18.6	15.5 (58)	9.1 (132)	15.6 (77)	1.04 (0.79,1.39)	0.768 <sup>c</sup>
f) Maximal (n=738)						0.408 <sup>b</sup>
	≤18.6	5.7 (105)	5.3 (190)	10.8 (83)	1.26 (0.93,1.70)	0.143 <sup>c</sup>
	>18.6	6.5 (77)	14.0 (179)	12.5 (104)	1.07 (0.86,1.33)	0.531 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
<b>Assumption</b>	<b>Time (Yrs.)</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>		<b>p-Value</b>	<b>Covariate Remarks</b>	
g) Minimal (n=520)				0.547 <sup>b</sup>	AGE (p=0.633)	
	≤18.6	1.20 (0.78,1.83)		0.408 <sup>c</sup>		
	>18.6	1.02 (0.76,1.38)		0.873 <sup>c</sup>		
h) Maximal (n=733)				0.329 <sup>b</sup>	AGE (p=0.852) ALC (p<0.001)	
	≤18.6	1.26 (0.92,1.73)		0.150 <sup>c</sup>		
	>18.6	1.04 (0.83,1.31)		0.716 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.



**TABLE 10-6. (Continued)**  
**Analysis of Other Disorders of the Liver**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	777	7.1	All Categories		0.087
Unknown	342	5.9	Unknown vs. Background	0.82 (0.48,1.38)	0.449
Low	196	9.2	Low vs. Background	1.33 (0.76,2.32)	0.319
High	187	11.8	High vs. Background	1.75 (1.04,2.95)	0.036
Total	1,502				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	777	All Categories		0.084	AGE (p=0.978) ALC (p<0.001)
Unknown	340	Unknown vs. Background	0.84 (0.49,1.44)	0.527	
Low	194	Low vs. Background	1.44 (0.82,2.53)	0.203	
High	186	High vs. Background	1.78 (1.03,3.07)	0.038	
Total	1,497				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

**TABLE 10-7.**  
**Analysis of Jaundice (Unspecified)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Yes</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=507)	Low	125	0.8	1.22 (0.52,2.86)	0.655
	Medium	255	0.4		
	High	127	0.8		
b) Maximal (n=721)	Low	183	2.2	0.83 (0.48,1.46)	0.507
	Medium	358	0.6		
	High	180	1.1		

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>			
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c) Minimal (n=507)	1.39 (0.60,3.19)	0.467	AGE (p=0.168)
d) Maximal (n=721)	0.90 (0.50,1.62)	0.722	AGE (p=0.060)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-7. (Continued)**  
**Analysis of Jaundice (Unspecified)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=507)	≤18.6	1.4 (72)	0.8 (126)	0.0 (52)	0.92 (0.23,3.59)	0.344 <sup>b</sup> 0.899 <sup>c</sup>
	>18.6	0.0 (53)	0.0 (130)	1.4 (74)	2.21 (0.60,8.15)	0.235 <sup>c</sup>
f) Maximal (n=721)	≤18.6	0.0 (105)	1.1 (189)	1.2 (81)	1.03 (0.42,2.56)	0.426 <sup>b</sup> 0.947 <sup>c</sup>
	>18.6	5.4 (74)	0.0 (172)	1.0 (100)	0.62 (0.27,1.42)	0.260 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=507)	≤18.6	1.25 (0.31,5.14)		0.454 <sup>b</sup> 0.754 <sup>c</sup>	AGE (p=0.117)	
	>18.6	2.44 (0.74,8.09)		0.144 <sup>c</sup>		
h) Maximal (n=721)	≤18.6	1.20 (0.46,3.11)		0.396 <sup>b</sup> 0.711 <sup>c</sup>	AGE (p=0.088)	
	>18.6	0.69 (0.29,1.62)		0.390 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-7. (Continued)**  
**Analysis of Jaundice (Unspecified)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	762	2.2	All Categories		0.056
Unknown	335	3.3	Unknown vs. Background	1.49 (0.69,3.21)	0.412
Low	193	0.0	Low vs. Background	--	0.042
High	181	1.1	High vs. Background	0.49 (0.11,2.14)	0.514
Total	1,471				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	762	All Categories		0.014	AGE (p=0.111)
Unknown	335	Unknown vs. Background	1.46 (0.67,3.15)	0.339	
Low	193	Low vs. Background	--	--	
High	181	High vs. Background	0.57 (0.13,2.50)	0.453	
Total	1,471				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin  $\leq$ 10 ppt.

Unknown (Ranch Hands): Current Dioxin  $\leq$ 10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq$ 33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

The change in significance between the unadjusted and adjusted results was due more to the choice of statistical method than to adjustment for age. A Pearson's chi-square p-value is presented for the unadjusted analysis because of sparse data; a likelihood ratio chi-square p-value is presented for the adjusted analysis. The likelihood ratio chi-square p-value based on an unadjusted analysis ( $p=0.011$ ) is comparable to the adjusted result.

### **Hepatomegaly**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Neither the unadjusted nor adjusted initial dioxin analyses of a post-SEA history of hepatomegaly were significant (Table 10-8 [a-d]:  $p>0.20$  for all analyses under both the minimal and maximal assumptions).

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant in either the unadjusted or adjusted analysis of hepatomegaly (Table 10-8 [e-h]:  $p>0.25$  for each analysis). The adjusted maximal analysis showed a marginally significant increased risk of hepatomegaly for Ranch Hands with a later tour (time $\leq$ 18.6: Adj. RR=1.67,  $p=0.065$ ). In this stratum, the percentages of hepatomegaly were 0.0, 2.6, and 3.6 percent for low, medium, and high current dioxin.

#### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis, the percentages of participants with a verified history of hepatomegaly did not differ significantly among current dioxin categories (Table 10-8 [i]: 2.2%, 0.9%, 3.1%, and 2.7% for the background, unknown, low, and high categories,  $p=0.230$ ). The adjusted analysis also did not show a significant overall difference (Table 10-8 [j]:  $p=0.136$ ).

### **Ulcer**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, initial dioxin was not associated significantly with the incidence of ulcer (Table 10-9 [a-d]:  $p>0.10$  for the unadjusted and adjusted analyses).

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The current dioxin-by-time since tour interaction was not significant for either the unadjusted or adjusted analysis of ulcer under both the minimal and maximal assumptions (Table 10-9 [e-h]:  $p>0.80$  for each analysis).

#### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of ulcer did not differ significantly among the four current dioxin categories in the unadjusted categorized current dioxin analysis (Table 10-9 [i]: 7.2%, 7.3%, 4.7%, and 8.7% for the background, unknown, low, and high categories,  $p=0.455$ ). The overall contrast was also not significant after covariate adjustment (Table 10-9 [j]:  $p=0.408$ ).

**TABLE 10-8.**  
**Analysis of Hepatomegaly**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Yes</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=520)	Low	130	2.3	0.90 (0.55,1.46)	0.657
	Medium	259	3.4		
	High	131	0.0		
b) Maximal (n=741)	Low	185	1.1	1.13 (0.80,1.61)	0.502
	Medium	371	2.4		
	High	185	2.2		

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>			
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c) Minimal (n=520)	1.01 (0.62,1.65)	0.954	AGE (p=0.028)
d) Maximal (n=741)	1.25 (0.87,1.80)	0.248	AGE (p=0.009)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-8. (Continued)

## Analysis of Hepatomegaly

Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=520)	≤18.6	2.8	4.7	0.0	0.93 (0.47,1.84)	0.830 <sup>c</sup>
		(72)	(128)	(54)		
	>18.6	0.0	3.8	0.0	0.98 (0.48,1.98)	0.944 <sup>c</sup>
		(58)	(131)	(77)		
f) Maximal (n=741)	≤18.6	0.0	2.6	3.6	1.37 (0.82,2.22)	0.266 <sup>c</sup>
		(106)	(191)	(83)		
	>18.6	1.3	2.2	1.9	0.98 (0.57,1.66)	0.928 <sup>c</sup>
		(79)	(179)	(103)		

Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=517)			0.964 <sup>b</sup>	AGE (p=0.013)
	≤18.6	1.17 (0.58,2.38)	0.665 <sup>c</sup>	
	>18.6	1.16 (0.58,2.31)	0.682 <sup>c</sup>	
h) Maximal (n=741)			0.298 <sup>b</sup>	AGE (p=0.004)
	≤18.6	1.67 (0.97,2.87)	0.065 <sup>c</sup>	
	>18.6	1.12 (0.65,1.93)	0.678 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-8. (Continued)**

**Analysis of Hepatomegaly**

<b>i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted</b>					
Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	785	2.2	All Categories		0.230
Unknown	345	0.9	Unknown vs. Background	0.40 (0.12,1.36)	0.142
Low	196	3.1	Low vs. Background	1.43 (0.56,3.67)	0.461
High	186	2.7	High vs. Background	1.25 (0.45,3.43)	0.667
Total	1,512				

<b>j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted</b>					
Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	785	All Categories		0.136	AGE (p=0.001) ALC (p=0.035)
Unknown	345	Unknown vs. Background	0.39 (0.11,1.33)	0.131	
Low	196	Low vs. Background	1.47 (0.57,3.79)	0.430	
High	186	High vs. Background	1.69 (0.60,4.75)	0.323	
Total	1,512				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
 High (Ranch Hands): Current Dioxin >33.3 ppt.



**TABLE 10-9.**  
**Analysis of Ulcer**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=514)	Low	128	5.5	1.12 (0.85,1.48)	0.430
	Medium	255	6.7		
	High	131	6.9		
b) Maximal (n=724)	Low	178	4.5	1.16 (0.94,1.43)	0.165
	Medium	360	6.4		
	High	186	7.0		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=514)	1.14 (0.86,1.52)	0.376	AGE (p=0.619)
d) Maximal (n=724)	1.18 (0.95,1.46)	0.143	AGE (p=0.595)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-9. (Continued)

## Analysis of Ulcer

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=514)	≤18.6	5.6 (71)	4.0 (125)	7.4 (54)	1.10 (0.67,1.83)	0.885 <sup>b</sup> 0.703 <sup>c</sup>
	>18.6	7.0 (57)	7.7 (130)	7.8 (77)	1.05 (0.74,1.50)	0.768 <sup>c</sup>
f) Maximal (n=724)	≤18.6	2.9 (104)	4.2 (189)	9.9 (81)	1.14 (0.80,1.63)	0.845 <sup>b</sup> 0.460 <sup>c</sup>
	>18.6	4.2 (72)	8.1 (174)	7.7 (104)	1.09 (0.83,1.44)	0.525 <sup>c</sup>
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=514)	≤18.6	1.12 (0.67,1.89)		0.875 <sup>b</sup> 0.661 <sup>c</sup>	AGE (p=0.771)	
	>18.6	1.07 (0.74,1.53)		0.720 <sup>c</sup>		
h) Maximal (n=724)	≤18.6	1.16 (0.81,1.66)		0.840 <sup>b</sup> 0.430 <sup>c</sup>	AGE (p=0.735)	
	>18.6	1.10 (0.83,1.46)		0.487 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-9. (Continued)**

**Analysis of Ulcer**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	764	7.2	All Categories		0.455
Unknown	331	7.3	Unknown vs. Background	1.01 (0.61,1.66)	0.976
Low	193	4.7	Low vs. Background	0.63 (0.31,1.30)	0.211
High	185	8.7	High vs. Background	1.22 (0.68,2.18)	0.502
Total	1,473				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	764	All Categories		0.408	AGE (p=0.285) IC (p=0.145)
Unknown	331	Unknown vs. Background	1.03 (0.62,1.69)	0.922	
Low	193	Low vs. Background	0.62 (0.30,1.28)	0.195	
High	185	High vs. Background	1.24 (0.69,2.25)	0.468	
Total	1,473				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
 High (Ranch Hands): Current Dioxin > 33.3 ppt.

## **Skin Bruises, Patches, or Sensitivity**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with the incidence of skin bruises, patches, or sensitivity (Table 10-10 [a-d]:  $p > 0.45$  for the unadjusted and adjusted analyses).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted current dioxin and time since tour analyses of skin bruises, patches, or sensitivity, the interaction between current dioxin and time was not significant under either the minimal (Table 10-10 [e]:  $p = 0.657$ ) or maximal (Table 10-10 [f]:  $p = 0.800$ ) assumption. The current dioxin-by-time interaction remained nonsignificant after adjustment for age and industrial chemical exposure (Table 10-10 [g] and [h]:  $p = 0.569$  under the minimal assumption and  $p = 0.741$  under the maximal assumption).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of skin bruises, patches, or sensitivity differed significantly among the current dioxin categories in the unadjusted analysis (Table 10-10 [i]: 18.4%, 25.8%, 27.8%, and 31.9% for the background, unknown, low, and high current dioxin categories,  $p < 0.001$ ). There was a highly significant increased risk of skin bruises, patches, or sensitivity in the three Ranch Hand current dioxin categories relative to the background category (unknown versus background: Est. RR=1.54, 95% C.I.: [1.14, 2.09],  $p = 0.005$ ; low versus background: Est. RR=1.72, 95% C.I.: [1.19, 2.47],  $p = 0.004$ ; high versus background: Est. RR=2.08, 95% C.I.: [1.45, 2.98],  $p < 0.001$ ). The adjusted analysis displayed similar findings. The overall contrast was highly significant (Table 10-10 [j]:  $p < 0.001$ ), as was each Ranch Hand versus background contrast (unknown versus background: Adj. RR=1.56, 95% C.I.: [1.15, 2.12],  $p = 0.005$ ; low versus background: Adj. RR=1.71, 95% C.I.: [1.19, 2.46],  $p = 0.004$ ; high versus background: Adj. RR=2.20, 95% C.I.: [1.52, 3.18],  $p < 0.001$ ).

## **Physical Examination Variable**

### **Current Hepatomegaly**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, initial dioxin was not associated significantly with the prevalence of hepatomegaly diagnosed at the 1987 physical examination in either the unadjusted or adjusted analysis (Table 10-11 [a-d]:  $p > 0.25$  for all analyses).

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The association between current dioxin and hepatomegaly did not differ significantly between time since tour strata for both the unadjusted and adjusted analyses (Table 10-11 [e-h]:  $p > 0.75$  for the minimal and maximal analyses).

#### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis for hepatomegaly diagnosed at the 1987 physical examination found a marginally significant overall contrast (Table 10-11 [i]:

**TABLE 10-10.**  
**Analysis of Skin Bruises, Patches, or Sensitivity**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=510)	Low	125	28.8	1.00 (0.86,1.17)	0.999
	Medium	255	29.4		
	High	130	33.1		
b) Maximal (n=724)	Low	178	28.1	1.04 (0.93,1.17)	0.484
	Medium	361	28.3		
	High	185	31.9		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=510)	1.03 (0.87,1.21)	0.753	AGE (p=0.032) IC (p=0.090)
d) Maximal (n=724)	1.04 (0.92,1.18)	0.508	AGE (p=0.027) IC (p=0.008)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-10. (Continued)**  
**Analysis of Skin Bruises, Patches, or Sensitivity**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=510)	≤18.6	26.9 (67)	31.8 (126)	31.5 (54)	1.06 (0.82,1.36)	0.657 <sup>b</sup> 0.659 <sup>c</sup>
	>18.6	31.6 (57)	26.9 (130)	34.2 (76)	0.98 (0.80,1.21)	0.869 <sup>c</sup>
f) Maximal (n=724)	≤18.6	24.3 (103)	31.5 (184)	31.7 (82)	1.08 (0.90,1.29)	0.800 <sup>b</sup> 0.396 <sup>c</sup>
	>18.6	23.7 (76)	29.0 (176)	32.0 (103)	1.05 (0.89,1.23)	0.572 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=510)	≤18.6	1.12 (0.86,1.46)		0.569 <sup>b</sup> 0.403 <sup>c</sup>	AGE (p=0.024) IC (p=0.101)	
	>18.6	1.02 (0.82,1.27)		0.880 <sup>c</sup>		
h) Maximal (n=724)	≤18.6	1.16 (0.81,1.66)		0.741 <sup>b</sup> 0.430 <sup>c</sup>	AGE (p=0.018) IC (p=0.012)	
	>18.6	1.10 (0.83,1.46)		0.487 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-10. (Continued)**  
**Analysis of Skin Bruises, Patches, and Sensitivity**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	768	18.4	All Categories		<0.001
Unknown	334	25.8	Unknown vs. Background	1.54 (1.14,2.09)	0.005
Low	194	27.8	Low vs. Background	1.72 (1.19,2.47)	0.004
High	185	31.9	High vs. Background	2.08 (1.45,2.98)	<0.001
Total	1,481				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	768	All Categories		<0.001	AGE (p=0.006) DC (p=0.091)
Unknown	334	Unknown vs. Background	1.56 (1.15,2.12)	0.005	
Low	194	Low vs. Background	1.71 (1.19,2.46)	0.004	
High	185	High vs. Background	2.20 (1.52,3.18)	<0.001	
Total	1,481				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

**TABLE 10-11.**  
**Analysis of Current Hepatomegaly**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=518)	Low	130	1.5	0.89 (0.50,1.59)	0.687
	Medium	258	2.7		
	High	130	0.0		
b) Maximal (n=738)	Low	184	0.5	1.23 (0.80,1.90)	0.361
	Medium	369	1.4		
	High	185	1.6		
Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
c) Minimal (n=518)	0.95 (0.53,1.71)		0.861	AGE (p=0.353)	
d) Maximal (n=738)	1.30 (0.83,2.02)		0.271	AGE (p=0.308)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.



**TABLE 10-11. (Continued)**  
**Analysis of Current Hepatomegaly**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=518)	≤18.6	1.4 (72)	4.0 (126)	0.0 (53)	0.99 (0.46,2.12)	0.986 <sup>b</sup> 0.973 <sup>c</sup>
	>18.6	0.0 (58)	2.3 (132)	0.0 (77)	0.98 (0.39,2.43)	0.959 <sup>c</sup>
f) Maximal (n=738)	≤18.6	0.0 (105)	1.6 (189)	3.7 (82)	1.41 (0.79,2.52)	0.800 <sup>b</sup> 0.244 <sup>c</sup>
	>18.6	0.0 (79)	0.6 (179)	1.9 (104)	1.25 (0.61,2.57)	0.537 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=518)	≤18.6	1.13 (0.51,2.51)		0.939 <sup>b</sup> 0.755 <sup>c</sup>	AGE (p=0.219)	
	>18.6	1.08 (0.44,2.67)		0.861 <sup>c</sup>		
h) Maximal (n=738)	≤18.6	1.59 (0.86,2.94)		0.756 <sup>b</sup> 0.137 <sup>c</sup>	AGE (p=0.175)	
	>18.6	1.37 (0.67,2.81)		0.389 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-11. (Continued)**  
**Analysis of Current Hepatomegaly**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	782	1.4	All Categories		0.052
Unknown	341	0.0	Unknown vs. Background	--	0.036
Low	194	1.6	Low vs. Background	1.10 (0.30,3.98)	0.999
High	186	2.7	High vs. Background	1.94 (0.66,5.64)	0.350
Total	1,503				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	782	All Categories		0.006	AGE (p=0.057)
Unknown	341	Unknown vs. Background	--	--	
Low	194	Low vs. Background	1.11 (0.31,4.04)	0.869	
High	186	High vs. Background	2.42 (0.81,7.29)	0.115	
Total	1,503				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.

Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.

Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .

High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

p=0.052). The percentages of participants who had hepatomegaly at the physical examination were 1.4, 0.0, 1.6, and 2.7 percent for the background, unknown, low, and high current dioxin categories. There were significantly fewer cases of hepatomegaly in the unknown category than in the background category (p=0.036).

The overall contrast was significant after adjusting for age (Table 10-11 [j]: p=0.006). However, the change in significance between the unadjusted and adjusted results was due partly to the choice of statistical method. A Pearson's chi-square p-value is presented for the unadjusted analysis because of sparse data; a likelihood ratio chi-square p-value is presented for the adjusted analysis. The likelihood ratio chi-square p-value based on an unadjusted analysis (p=0.011) is similar to the adjusted finding.

### ***Laboratory Variables***

#### **AST (Continuous)**

##### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analysis of AST in its continuous form was not significant for either the minimal (Table 10-12 [a]: p=0.878) or maximal (Table 10-12 [b]: p=0.304) analysis.

Under the minimal assumption, the adjusted analysis found a significant initial dioxin-by-degreasing chemical exposure interaction (Table 10-12 [c]: p=0.042). Exploration of this interaction showed a nonsignificant positive association between AST and initial dioxin for Ranch Hands who had never been exposed to degreasing chemicals (Appendix Table I-1: p=0.121) that contrasted with a nonsignificant negative association between AST and initial dioxin for Ranch Hands who had been exposed to degreasing chemicals (p=0.180).

Excluding the initial dioxin-by-degreasing chemical interaction, the adjusted minimal analysis did not reveal a significant association between AST and initial dioxin (Table 10-12 [c]: p=0.767). The adjusted maximal analysis also did not show a significant initial dioxin effect (Table 10-12 [d]: p=0.369).

##### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The association between current dioxin and AST did not differ significantly between time since tour strata based on the unadjusted analyses for both the minimal and maximal assumptions (Table 10-12 [e] and [f]: p=0.599 and p=0.758).

The interaction between current dioxin and time remained nonsignificant for the adjusted minimal analysis (Table 10-12 [g]: p=0.576), but the interaction among current dioxin, time, and current alcohol use was significant for the adjusted maximal analysis (Table 10-12 [h]: p=0.002). The current alcohol use covariate was dichotomized to explore the interaction. Stratified results showed that the current dioxin-by-time interaction was not significant for Ranch Hands who currently consume one alcoholic beverage per day or less (Appendix Table I-1: p=0.225). However, the interaction was significant for Ranch Hands who currently consume more than one drink per day (p=0.031). There was a significant negative

**TABLE 10-12.**  
**Analysis of AST (U/L) (Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> <0.001)	Low	130	26.86	0.0018 (0.0116)	0.878
	Medium	257	25.78		
	High	130	26.01		
b) Maximal (n=737) (R <sup>2</sup> =0.001)	Low	184	24.85	0.0087 (0.0085)	0.304
	Medium	368	26.36		
	High	185	25.98		

  

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=511) (R <sup>2</sup> =0.122)	Low	130	27.14**	-0.0033 (0.0113)**	0.767**	INIT*DC (p=0.042) ALC*RACE (p=0.002) ALC*DRKYR (p=0.029)
	Medium	253	26.15**			
	High	128	26.20**			
d) Maximal (n=728) (R <sup>2</sup> =0.126)	Low	182	24.73	0.0076 (0.0084)	0.369	AGE*RACE (p=0.032) RACE*ALC (p=0.035) RACE*IC (p=0.023) ALC*DRKYR (p=0.035) ALC*IC (p=0.035)
	Medium	365	26.18			
	High	181	25.64			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm AST versus log<sub>2</sub> dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

INIT: Log<sub>2</sub> (initial dioxin).

**TABLE 10-12. (Continued)**  
**Analysis of AST (U/L) (Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.012)	≤18.6	25.59 (72)	25.11 (126)	24.97 (53)	0.0038 (0.0189)	0.599 <sup>c</sup> 0.840 <sup>d</sup>	
	>18.6	28.65 (58)	26.50 (131)	26.55 (77)	-0.0090 (0.0154)	0.559 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.009)	≤18.6	25.49 (105)	24.85 (189)	25.53 (82)	0.0018 (0.0132)	0.758 <sup>c</sup> 0.889 <sup>d</sup>	
	>18.6	24.23 (79)	27.72 (178)	26.73 (104)	0.0072 (0.0116)	0.532 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=511) (R <sup>2</sup> =0.140)	≤18.6	25.19 (72)	24.78 (125)	24.52 (52)	-0.0022 (0.0179)	0.576 <sup>c</sup> 0.904 <sup>d</sup>	DC (p=0.083) RACE*ALC (p<0.001) RACE*IC (p=0.019)
	>18.6	28.30 (58)	26.52 (128)	26.33 (76)	-0.0150 (0.0150)	0.316 <sup>d</sup>	ALC*DRKYR (p=0.020)
h) Maximal (n=728) (R <sup>2</sup> =0.143)	≤18.6	**** (104)	**** (188)	**** (80)	****	**** ****	CURR*TIME*ALC (p=0.002) DC (p=0.071)
	>18.6	**** (78)	**** (176)	**** (102)	****	**** ****	AGE*RACE (p=0.010) RACE*IC (p=0.018) ALC*DRKYR (p<0.001)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm AST versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

\*\*\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (p≤0.01); adjusted mean, adjusted slope, standard error, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

CURR: Log<sub>2</sub> (current dioxin).

TIME: Time since tour.

**TABLE 10-12. (Continued)**  
**Analysis of AST (U/L) (Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	25.70	All Categories		0.276
Unknown	341	24.93	Unknown vs. Background	-0.77 --	0.120
Low	193	25.46	Low vs. Background	-0.24 --	0.704
High	186	26.20	High vs. Background	0.50 --	0.434
Total	1,499		(R <sup>2</sup> =0.003)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	779	26.37	All Categories		0.374	RACE (p=0.075) ALC (p<0.001)
Unknown	339	25.71	Unknown vs. Background	-0.66 --	0.189	
Low	191	26.32	Low vs. Background	-0.05 --	0.943	
High	185	26.90	High vs. Background	0.53 --	0.409	
Total	1,494		(R <sup>2</sup> =0.045)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>p-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

association between current dioxin and AST for these Ranch Hands who had an early tour (time>18.6:  $p=0.006$ ). The adjusted mean AST levels for this stratum were 27.06, 32.99, and 25.34 U/L. For Ranch Hands who had a later tour, there was a nonsignificant positive association (time≤18.6:  $p=0.647$ ).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The mean levels of AST did not differ significantly among the four current dioxin categories for either the unadjusted or adjusted analysis of categorized current dioxin (Table 10-12 [i] and [j]:  $p=0.276$  and  $p=0.374$ , respectively).

**AST (Discrete)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, the prevalence of abnormally high levels of AST was not associated significantly with initial dioxin in the unadjusted analyses (Table 10-13 [a] and [b]:  $p=0.999$  and  $p=0.720$ , respectively).

The adjusted minimal analysis detected two significant initial dioxin-by-covariate interactions (Table 10-13 [c]: initial dioxin-by-race,  $p=0.019$  and initial dioxin-by-degreasing chemical exposure,  $p=0.029$ ). To explore these interactions, separate analyses were done for Blacks and non-Blacks. The association between initial dioxin and discretized AST was significant for Blacks (Appendix Table I-1:  $p=0.010$ ), even though only three Blacks had an abnormally high AST level, all in the low initial dioxin category. For non-Blacks, the initial dioxin-by-degreasing chemical exposure interaction was significant ( $p=0.039$ ). The relative risk was marginally more than 1 for non-Black Ranch Hands who had never been exposed to degreasing chemicals (Adj. RR=1.97,  $p=0.069$ ). By contrast, the relative risk was less than 1, but not significant, for non-Black Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.82,  $p=0.340$ ). The adjusted relative risk of an abnormal level of AST was not significant (Table 10-13 [c]: Adj. RR=0.88,  $p=0.479$ ) after deleting the two initial dioxin-by-covariate interactions.

In the adjusted maximal analysis, the initial dioxin-by-degreasing chemical exposure interaction was significant (Table 10-13 [d]:  $p=0.045$ ). For Ranch Hands who had never been exposed to degreasing chemicals, the relative risk of an abnormal level of AST was marginally more than 1 (Appendix Table I-1: Adj. RR=1.60,  $p=0.086$ ). This contrasted with a nonsignificant relative risk less than 1 for Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.85,  $p=0.258$ ). After excluding the interaction, the relative risk was not significant (Table 10-13 [d]: Adj. RR=0.96,  $p=0.737$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not significant for the unadjusted and adjusted analyses of discretized AST (Table 10-13 [e-h]:  $p>0.30$  for all analyses).

**TABLE 10-13.**  
**Analysis of AST (Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	6.9	1.00 (0.72,1.40)	0.999
	Medium	257	3.5		
	High	130	5.4		
b) Maximal (n=737)	Low	184	3.8	1.05 (0.82,1.33)	0.720
	Medium	368	5.7		
	High	185	4.3		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=514)	0.88 (0.62,1.25)**	0.479**	INIT*RACE (p=0.019) INIT*DC (p=0.029) ALC (p<0.001)
d) Maximal (n=732)	0.96 (0.75,1.23)**	0.737**	INIT*DC (p=0.045) ALC (p<0.001)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.



TABLE 10-13. (Continued)

## Analysis of AST (Discrete)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	5.6 (72)	3.2 (126)	1.9 (53)	0.80 (0.40,1.59)	0.467 <sup>b</sup> 0.520 <sup>c</sup>
	>18.6	10.3 (58)	3.1 (131)	7.8 (77)	1.06 (0.72,1.57)	0.760 <sup>c</sup>
f) Maximal (n=737)	≤18.6	3.8 (105)	3.2 (189)	3.7 (82)	0.96 (0.61,1.51)	0.800 <sup>b</sup> 0.853 <sup>c</sup>
	>18.6	3.8 (79)	7.9 (178)	5.8 (104)	1.03 (0.77,1.37)	0.858 <sup>c</sup>
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=514)	≤18.6	0.65 (0.30,1.39)		0.368 <sup>b</sup> 0.263 <sup>c</sup>	ALC (p<0.001)	
	>18.6	0.95 (0.63,1.42)		0.789 <sup>c</sup>	DC (p=0.078)	
h) Maximal (n=732)	≤18.6	0.88 (0.54,1.44)		0.922 <sup>b</sup> 0.607 <sup>c</sup>	ALC (p<0.001)	
	>18.6	0.90 (0.66,1.23)		0.527 <sup>c</sup>	DC (p=0.019)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-13. (Continued)**

**Analysis of AST (Discrete)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	3.6	All Categories		0.832
Unknown	341	3.5	Unknown vs. Background	0.98 (0.49,1.95)	0.950
Low	193	3.1	Low vs. Background	0.86 (0.35,2.11)	0.743
High	186	4.8	High vs. Background	1.36 (0.63,2.94)	0.429
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.959	ALC (p<0.001) DC (p=0.065)
Unknown	339	Unknown vs. Background	1.05 (0.51,2.15)	0.893	
Low	191	Low vs. Background	0.93 (0.38,2.30)	0.877	
High	185	High vs. Background	1.22 (0.55,2.72)	0.623	
Total	1,494				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The prevalence of abnormally high levels of AST did not differ significantly among the four current dioxin categories for either the unadjusted or adjusted analysis (Table 10-13 [i] and [j]:  $p=0.832$  and  $p=0.959$ ).

**ALT (Continuous)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analysis displayed a significant positive association with ALT under both the minimal and maximal assumptions (Table 10-14 [a] and [b]:  $p=0.039$  and  $p<0.001$ ). The mean levels of ALT were 21.15, 21.50, and 22.99 U/L for the low, medium, and high minimal initial dioxin categories. For the maximal cohort, the means for the low, medium, and high initial dioxin categories were 18.86, 21.47, and 22.63 U/L.

After covariate adjustment, the association between initial dioxin and ALT became nonsignificant for the minimal cohort (Table 10-14 [c]:  $p=0.190$ ). This change in significance was due primarily to the adjustment for age (ALT levels decreased significantly with age; age is associated positively with dioxin, see Chapter 5, Covariate Associations). The adjusted analysis for the maximal cohort detected a significant initial dioxin-by-age interaction (Table 10-14 [d]:  $p=0.047$ ). Age was dichotomized to explore the interaction. Stratified results showed a highly significant positive association between ALT and initial dioxin for younger Ranch Hands, those born in or after 1942 (Appendix Table I-1:  $p<0.001$ ). For these Ranch Hands, the adjusted mean levels of ALT for the low, medium, and high initial dioxin categories were 18.29, 21.45, and 23.61 U/L. The association between ALT and initial dioxin was not significant for Ranch Hands born before 1942 ( $p=0.646$ ).

After excluding the initial dioxin-by-age interaction, the adjusted results for the maximal cohort paralleled the unadjusted findings, exhibiting a significant positive association between ALT and initial dioxin (Table 10-14 [d]:  $p=0.005$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the unadjusted analysis of current dioxin and time since tour did not find a significant interaction between current dioxin and time for ALT (Table 10-14 [e] and [f]:  $p=0.464$  and  $p=0.989$ , respectively). Although the association between current dioxin and ALT did not differ significantly between time strata, the association was significant within each stratum under the maximal assumption (time $\leq$ 18.6: slope=0.0472,  $p=0.022$ ; time $>$ 18.6: slope=0.0468,  $p=0.010$ ). Under the minimal assumption, the association between current dioxin and ALT was marginally significant for Ranch Hands with an early tour (time $\leq$ 18.6:  $p=0.073$ ).

The current dioxin-by-time interaction remained nonsignificant for the adjusted minimal analysis (Table 10-14 [g]:  $p=0.531$ ), but the adjusted maximal analysis detected a significant current dioxin-by-time-by-current alcohol use interaction (Table 10-14 [h]:  $p=0.026$ ). Current alcohol use was dichotomized ( $\leq$ 1 drink/day and  $>$ 1 drink/day) to explore the interaction. Appendix Table I-1 presents stratified results that show a marginally significant interaction between current dioxin and time for Ranch Hands who currently consume more than one alcoholic drink per day ( $p=0.068$ ). However, for these Ranch Hands,

**TABLE 10-14.**  
**Analysis of ALT (U/L) (Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> =0.008)	Low	130	21.15	0.0372 (0.0179)	0.039
	Medium	257	21.50		
	High	130	22.99		
b) Maximal (n=737) (R <sup>2</sup> =0.017)	Low	184	18.86	0.0475 (0.0132)	<0.001
	Medium	368	21.47		
	High	185	22.63		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=514) (R <sup>2</sup> =0.088)	Low	130	20.20	0.0239 (0.0182)	0.190	AGE (p<0.001) RACE*IC (p=0.007) ALC*IC (p=0.004)
	Medium	255	20.35			
	High	129	21.26			
d) Maximal (n=732) (R <sup>2</sup> =0.097)	Low	183	17.97**	0.0379 (0.0133)**	0.005**	INIT*AGE (p=0.047) DC (p=0.145) RACE*IC (p=0.005) ALC*IC (p=0.013)
	Medium	365	20.57**			
	High	184	20.82**			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm ALT versus log<sub>2</sub> dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-14. (Continued)**  
**Analysis of ALT (U/L) (Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517) (R <sup>2</sup> =0.011)	≤18.6	20.02 (72)	21.36 (126)	22.30 (53)	0.0525 (0.0293)	0.464 <sup>c</sup> 0.073 <sup>d</sup>
	>18.6	22.65 (58)	21.68 (131)	23.37 (77)	0.0249 (0.0239)	0.298 <sup>d</sup>
f) Maximal (n=737) (R <sup>2</sup> =0.018)	≤18.6	19.63 (105)	20.34 (189)	22.47 (82)	0.0472 (0.0205)	0.989 <sup>c</sup> 0.022 <sup>d</sup>
	>18.6	17.74 (79)	22.46 (178)	23.37 (104)	0.0468 (0.0181)	0.010 <sup>d</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=514) (R <sup>2</sup> =0.093)	≤18.6	19.04 (72)	19.80 (126)	19.83 (52)	0.0283 (0.0296)	0.531 <sup>c</sup> 0.339 <sup>d</sup>	AGE (p<0.001) RACE*IC (p=0.006) ALC*IC (p=0.005)
	>18.6	22.11 (58)	20.68 (129)	21.75 (77)	0.0053 (0.0241)	0.825 <sup>d</sup>	
h) Maximal (n=732) (R <sup>2</sup> =0.091)	≤18.6	18.56** (105)	19.59** (188)	20.66** (81)	0.0355 (0.0206)**	0.872*** <sup>c</sup> 0.086*** <sup>d</sup>	CURR*TIME*ALC (p=0.026) AGE (p=0.005)
	>18.6	17.69** (78)	21.98** (176)	22.03** (104)	0.0312 (0.0183)**	0.088*** <sup>d</sup>	RACE*IC (p=0.007)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm ALT versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-14. (Continued)**  
**Analysis of ALT (U/L) (Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	20.62	All Categories		<0.001
Unknown	341	19.06	Unknown vs. Background	-1.56 --	0.011
Low	193	21.01	Low vs. Background	0.39 --	0.634
High	186	22.97	High vs. Background	2.35 --	0.006
Total	1,499		(R <sup>2</sup> =0.012)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	777	20.34**	All Categories		0.012**	DXCAT*DRKYR (p=0.017)
Unknown	338	19.16**	Unknown vs. Background	-1.18 -- **	0.055**	AGE (p<0.001)
Low	191	20.83**	Low vs. Background	0.49 -- **	0.531**	DC (p=0.067)
High	182	22.09**	High vs. Background	1.75 -- **	0.035**	IC (p=0.104)
Total	1,488		(R <sup>2</sup> =0.050)			RACE*ALC (p=0.001)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>p-value is based on difference of means on natural logarithm scale.

\*\*Categorized current dioxin-by-covariate interaction (0.01<p≤0.05); adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

DXCAT: Categorized current dioxin (categorized within group).

the association between current dioxin and ALT was not significant within either time stratum (time $\leq$ 18.6: Adj. slope=0.0552, p=0.257; time $>$ 18.6: Adj. slope=-0.0603, p=0.140).

By contrast, the interaction between current dioxin and time was not significant for Ranch Hands who currently consume no more than one drink per day (p=0.388), but the association between current dioxin and ALT was significant for these Ranch Hands with an early tour (time $>$ 18.6: Adj. slope=0.0593, p=0.003; Adj. means: 16.45, 20.48, and 21.86 U/L for low, medium, and high current dioxin). After excluding the interaction, the current dioxin-by-time interaction was not significant in the adjusted maximal analysis (Table 10-14 [h]: p=0.872), but the association between current dioxin and ALT was marginally significant for each time stratum (time $\leq$ 18.6: p=0.086; time $>$ 18.6: p=0.088).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted analysis of categorized current dioxin found a significant overall difference among mean levels of ALT (Table 10-14 [i]: 20.62, 19.06, 21.01, and 22.97 U/L for the background, unknown, low, and high current dioxin categories, p<0.001). The mean for the unknown category was significantly less than the background mean (p=0.011), and the mean for the high current dioxin category was significantly more than the background mean (p=0.006).

The adjusted analysis detected a significant categorized current dioxin-by-lifetime alcohol history interaction (Table 10-14 [j]: p=0.017). The lifetime alcohol history covariate was trichotomized into never (0 drink-years), moderate (>0-40 drink-years), and heavy (>40 drink-years) to explore the interaction. The mean levels of ALT did not differ significantly among current dioxin categories for participants who had never drunk alcohol (Appendix Table I-1: p=0.434). For moderate lifetime drinkers, there was a significant overall difference among category means (20.28, 18.13, 21.30, and 21.07 U/L for the background, unknown, low, and high current dioxin categories, p=0.002). In this stratum, the mean for the unknown category was significantly less than the background mean (p=0.002), but the means for the low and high categories did not differ significantly from the background mean (p=0.280 and p=0.443, respectively). The overall contrast was of borderline significance for heavy lifetime drinkers (p=0.057). The adjusted means in this stratum were 19.95, 22.78, 19.98, and 23.93 U/L for the background, unknown, low, and high current dioxin categories. The mean for the high category was significantly more than the background mean (p=0.024) and the mean for the unknown category was marginally more than the background mean (p=0.062).

After excluding the interaction, the adjusted mean levels of ALT differed significantly among the four current dioxin categories (Table 10-14 [j]: 20.34, 19.16, 20.83, and 22.09 U/L, for the background, unknown, low, and high current dioxin categories, p=0.012). The mean ALT for the unknown category was marginally less than the background mean (p=0.055), and the mean ALT for the high category was significantly more than the background mean (p=0.035).

## **ALT (Discrete)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under the minimal assumption, discretized ALT was not associated significantly with initial dioxin in the unadjusted analysis (Table 10-15 [a]:  $p=0.235$ ). However, for the maximal assumption, the unadjusted analysis revealed a significant relative risk (Table 10-15 [b]: Est. RR=1.18,  $p=0.031$ ). The percentage of abnormally high ALT values increased with levels of initial dioxin (8.2%, 13.3%, and 14.6% for the low, medium, and high maximal cohort initial dioxin categories).

The adjusted analyses revealed a significant initial dioxin-by-covariate interaction for each cohort. The adjusted minimal analysis found a significant initial dioxin-by-degreasing chemical interaction (Table 10-15 [c]:  $p=0.011$ ). Stratified results showed that the prevalence of abnormally high ALT levels was associated significantly with initial dioxin for Ranch Hands who had never been exposed to degreasing chemicals (Appendix Table I-1: Adj. RR=1.62,  $p=0.013$ ). The relative risk was less than 1, but not significant, for Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.90,  $p=0.433$ ). The initial dioxin effect was not significant ( $p=0.509$ ) after excluding the interaction between initial dioxin and degreasing chemical exposure.

The adjusted maximal analysis found a significant initial dioxin-by-current alcohol use interaction (Table 10-15 [d]:  $p=0.035$ ). Current alcohol use was trichotomized to explore the interaction. Appendix Table I-1 shows that the relative risk was significantly more than 1 for Ranch Hands who currently consume at most one alcoholic drink per day (Adj. RR=1.28,  $p=0.007$ ; % abnormal: 6.3%, 10.3%, and 14.8% for the low, medium, and high initial dioxin categories). The relative risk was less than 1, but not significant, for the other current alcohol use strata (>1-4: Adj. RR=0.95,  $p=0.774$ ; >4: Adj. RR=0.67,  $p=0.371$ ). After excluding the interaction, the association between initial dioxin and ALT was marginally significant (Table 10-15 [d]: Est. RR=1.15,  $p=0.079$ ).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The unadjusted current dioxin and time since tour analyses for discretized ALT did not find a significant current dioxin-by-time interaction for either the minimal (Table 10-15 [e]:  $p=0.267$ ) or maximal (Table 10-15 [f]:  $p=0.338$ ) cohorts. However, for Ranch Hands with a later tour, the estimated relative risk of an abnormally high level of ALT was marginally significant for the minimal cohort (time $\leq$ 18.6: Est. RR=1.33,  $p=0.082$ ; % abnormal: 6.9%, 15.1%, and 17.0% for the low, medium, and high current dioxin categories) and significant for the maximal cohort (Est. RR=1.30,  $p=0.028$ ; % abnormal: 9.5%, 11.6%, and 14.6% for the low, medium, and high current dioxin categories).

After covariate adjustment, the current dioxin-by-time interaction remained nonsignificant for both cohorts (Table 10-15 [g] and [h]:  $p=0.230$  and  $p=0.248$  for the minimal and maximal cohorts). For Ranch Hands with a later tour, the adjusted relative risk was marginally significant in the maximal analysis (Adj. RR=1.27,  $p=0.062$ ).



**TABLE 10-15.**  
**Analysis of ALT (Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	12.3	1.13 (0.93,1.38)	0.235
	Medium	257	12.8		
	High	130	16.2		
b) Maximal (n=737)	Low	184	8.2	1.18 (1.02,1.38)	0.031
	Medium	368	13.3		
	High	185	14.6		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=514)	1.07 (0.87,1.33)**	0.509**	INIT*DC (p=0.011) ALC (p=0.039) AGE*RACE (p=0.037)
d) Maximal (n=732)	1.15 (0.98,1.35)**	0.079**	INIT*ALC (p=0.035) RACE*AGE (p=0.018)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-15. (Continued)

## Analysis of ALT (Discrete)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	6.9 (72)	15.1 (126)	17.0 (53)	1.33 (0.96,1.84)	0.267 <sup>b</sup> 0.082 <sup>c</sup>
	>18.6	15.5 (58)	12.2 (131)	15.6 (77)	1.05 (0.80,1.37)	0.729 <sup>c</sup>
f) Maximal (n=737)	≤18.6	9.5 (105)	11.6 (189)	14.6 (82)	1.30 (1.03,1.66)	0.338 <sup>b</sup> 0.028 <sup>c</sup>
	>18.6	5.1 (79)	15.2 (178)	15.4 (104)	1.12 (0.91,1.37)	0.285 <sup>c</sup>
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=514) (p=0.022)	≤18.6	1.26 (0.89,1.78)		0.230 <sup>b</sup> 0.197 <sup>c</sup>	ALC (p=0.046) AGE*RACE	
	>18.6	0.96 (0.73,1.28)		0.799 <sup>c</sup>		
h) Maximal (n=732) (p=0.015)	≤18.6	1.27 (0.99,1.63)		0.248 <sup>b</sup> 0.062 <sup>c</sup>	ALC (p<0.001) AGE*RACE	
	>18.6	1.05 (0.85,1.30)		0.651 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-15. (Continued)****Analysis of ALT (Discrete)****i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	10.9	All Categories		0.197
Unknown	341	9.4	Unknown vs. Background	0.85 (0.55,1.30)	0.442
Low	193	13.5	Low vs. Background	1.27 (0.79,2.04)	0.318
High	186	15.1	High vs. Background	1.45 (0.91,2.29)	0.116
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.391	AGE (p=0.002) ALC (p<0.001)
Unknown	339	Unknown vs. Background	0.89 (0.58,1.37)	0.592	
Low	191	Low vs. Background	1.32 (0.82,2.12)	0.256	
High	185	High vs. Background	1.29 (0.81,2.07)	0.282	
Total	1,494				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The overall contrast was not significant for either the unadjusted or adjusted categorized current dioxin analysis of discretized ALT (Table 10-15 [i] and [j]:  $p=0.197$  and  $p=0.391$ , respectively). Also, none of the three Ranch Hand versus background contrasts was significant in either analysis.

**GGT (Continuous)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analysis of GGT in its continuous form was not significant for the minimal cohort (Table 10-16 [a]:  $p=0.357$ ), but a highly significant positive association was evident for the maximal cohort (Table 10-16 [b]:  $p<0.001$ ). The mean levels of GGT were 28.34, 35.47, and 35.90 U/L for the low, medium, and high initial dioxin categories under the maximal assumption.

The adjusted results paralleled the unadjusted findings. No significant association was found between GGT and initial dioxin for the minimal cohort (Table 10-16 [c]:  $p=0.338$ ), but the association was highly significant for the adjusted maximal analysis (Table 10-16 [d]:  $p<0.001$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The unadjusted association between GGT and current dioxin did not differ significantly between time since tour strata for either the minimal or maximal cohort (Table 10-16 [e] and [f]:  $p=0.715$  and  $p=0.537$ ). However, for the maximal cohort, the unadjusted association between GGT and current dioxin was significant within each time stratum (time $\leq$ 18.6: slope=0.0701,  $p=0.011$ ; time $>$ 18.6: slope=0.0476,  $p=0.048$ ). The mean levels of GGT for the low, medium, and high categories were 28.17, 32.77, and 36.42 U/L for Ranch Hands with a later tour, and 28.40, 37.66, and 37.13 U/L for Ranch Hands with an early tour.

For both cohorts, the interaction between current dioxin and time remained nonsignificant in the adjusted analyses (Table 10-16 [g] and [h]:  $p=0.718$  and  $p=0.305$  for the minimal and maximal cohorts). For the maximal cohort, the adjusted association between GGT and current dioxin was significantly positive for Ranch Hands with a later tour (time $\leq$ 18.6:  $p=0.003$ ) and marginally positive for Ranch Hands with an early tour (time $>$ 18.6:  $p=0.062$ ).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The mean levels of GGT differed significantly among the four current dioxin categories for the unadjusted analysis of categorized current dioxin (Table 10-16 [i]: 32.03, 28.75, 34.99, and 36.82 U/L for the background, unknown, low, and high current dioxin categories,  $p<0.001$ ). Each of the contrasts relative to the background category was significant or marginally significant. Comparable to the findings for ALT, the mean for the unknown current dioxin category was significantly less than the background mean ( $p=0.009$ ) and the mean for the high category was significantly more than the background mean ( $p=0.007$ ). The low current dioxin category mean was marginally more than the background category mean ( $p=0.083$ ).

**TABLE 10-16.**  
**Analysis of GGT (U/L)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> =0.002)	Low	130	35.56	0.0230 (0.0249)	0.357
	Medium	257	35.81		
	High	130	35.94		
b) Maximal (n=737) (R <sup>2</sup> =0.017)	Low	184	28.34	0.0616 (0.0175)	<0.001
	Medium	368	35.47		
	High	185	35.90		

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=514) (R <sup>2</sup> =0.096)	Low	130	35.60	0.0232 (0.0242)	0.338	ALC*IC (p=0.021)
	Medium	255	35.81			
	High	129	36.60			
d) Maximal (n=732) (R <sup>2</sup> =0.121)	Low	183	30.45	0.0636 (0.0169)	<0.001	RACE (p=0.092) ALC*IC (p<0.001)
	Medium	365	38.05			
	High	184	38.88			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm GGT versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-16. (Continued)**  
**Analysis of GGT (U/L) (Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.004)	≤18.6	33.55 (72)	35.44 (126)	33.41 (53)	0.0289 (0.0406)	0.715 <sup>c</sup> 0.477 <sup>d</sup>	
	>18.6	39.09 (58)	36.14 (131)	37.22 (77)	0.0097 (0.0332)	0.770 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.019)	≤18.6	28.17 (105)	32.77 (189)	36.42 (82)	0.0701 (0.0273)	0.537 <sup>c</sup> 0.011 <sup>d</sup>	
	>18.6	28.40 (79)	37.66 (178)	37.13 (104)	0.0476 (0.0240)	0.048 <sup>d</sup>	
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=514) (R <sup>2</sup> =0.098)	≤18.6	33.52 (72)	35.89 (126)	34.55 (52)	0.0308 (0.0392)	0.718 <sup>c</sup> 0.432 <sup>d</sup>	ALC*IC (p=0.024)
	>18.6	38.69 (58)	35.84 (129)	37.41 (77)	0.0127 (0.0321)	0.693 <sup>d</sup>	
h) Maximal (n=732) (R <sup>2</sup> =0.124)	≤18.6	29.89 (105)	35.72 (188)	39.78 (81)	0.0790 (0.0263)	0.305 <sup>c</sup> 0.003 <sup>d</sup>	RACE (p=0.092) ALC*IC (p=0.001)
	>18.6	31.60 (78)	40.07 (176)	39.61 (104)	0.0434 (0.0232)	0.062 <sup>d</sup>	

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm GGT versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-16. (Continued)**  
**Analysis of GGT (U/L) (Continuous)**

<b>i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted</b>						
Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>		p-Value <sup>f</sup>
Background	779	32.03	All Categories			<0.001
Unknown	341	28.75	Unknown vs. Background	-3.28 --		0.009
Low	193	34.99	Low vs. Background	2.96 --		0.083
High	186	36.82	High vs. Background	4.79 --		0.007
Total	1,499		(R <sup>2</sup> =0.015)			

  

<b>j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted</b>						
Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>		Covariate Remarks
Background	777	34.64	All Categories		<0.001	RACE (p=0.008) ALC*DRKYR
Unknown	338	31.49	Unknown vs. Background	-3.15 --	0.017	(p<0.001)
Low	191	38.28	Low vs. Background	3.64 --	0.043	
High	182	40.82	High vs. Background	6.18 --	0.001	
Total	1,488		(R <sup>2</sup> =0.088)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

The results of the adjusted analysis displayed similar findings. The overall contrast remained highly significant (Table 10-16 [j]:  $p < 0.001$ ). The adjusted mean levels of GGT for the background, unknown, low, and high current dioxin categories were 34.64, 31.49, 38.28, and 40.82 U/L. The mean for the unknown current dioxin category was significantly less than the background mean ( $p = 0.017$ ) and the means for the low and high current dioxin category were significantly more than the background mean ( $p = 0.043$  and  $p = 0.001$ , respectively).

### **GGT (Discrete)**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under the minimal assumption, the prevalence of abnormally high levels of GGT was not associated significantly with initial dioxin based on the unadjusted analysis (Table 10-17 [a]:  $p = 0.574$ ). However, the unadjusted maximal analysis found a marginally significant positive association between discretized GGT and initial dioxin (Table 10-17 [b]: Est. RR=1.20,  $p = 0.052$ ). The percentage of abnormal GGT values increased with initial dioxin for the maximal cohort (4.9%, 9.5%, and 9.7% for the low, medium, and high initial dioxin categories).

The adjusted initial dioxin analyses of discretized GGT detected significant initial dioxin-by-covariate interactions that also were present in the adjusted analyses of discretized AST. The adjusted minimal analysis found a significant initial dioxin-by-race interaction and a significant initial dioxin-by-degreasing chemical exposure interaction (Table 10-17 [c]:  $p = 0.043$  and  $p = 0.006$ , respectively). Comparable to the AST analysis, separate analyses were done for Blacks and non-Blacks to explore the interactions. Appendix Table I-1 presents stratified results. The association between initial dioxin and discretized GGT was marginally significant for Blacks (Appendix Table I-1:  $p = 0.055$ ). Only three Blacks had an abnormally high GGT, all in the low initial dioxin category. The initial dioxin-by-degreasing chemical interaction was significant for non-Blacks ( $p = 0.009$ ). The association between initial dioxin and GGT was significantly more than 1 for non-Black Ranch Hands who had never been exposed to degreasing chemicals (Adj. RR=1.65,  $p = 0.010$ ). The percentages of abnormal levels of GGT for these Ranch Hands were 7.3, 10.4, and 25.9 percent for the low, medium, and high initial dioxin categories. The adjusted relative risk was less than 1, but not significant, for non-Black Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.85,  $p = 0.336$ ). After excluding the interactions, the adjusted relative risk was not significant for the minimal cohort (Table 10-17 [c]: Adj. RR=1.10,  $p = 0.437$ ).

The adjusted maximal analyses for discretized GGT detected a significant initial dioxin-by-degreasing chemical interaction (Table 10-17 [d]:  $p = 0.005$ ), that was also noted in the adjusted maximal analysis of discretized AST. Appendix Table I-1 presents stratified results that show a significant relative risk for Ranch Hands who had never been exposed to degreasing chemicals (Est. RR=1.76,  $p < 0.001$ ; % abnormal: 3.5%, 8.0%, and 22.7%, for the low, medium, and high initial dioxin categories), in contrast to a nonsignificant relative risk for Ranch Hands who had been exposed to degreasing chemicals (Est. RR=1.01,  $p = 0.930$ ). After deleting the interaction, the adjusted maximal analysis displayed a significant increased risk of an abnormally high GGT level (Table 10-17 [d]: Adj. RR=1.24,  $p = 0.028$ ).



**TABLE 10-17.**

**Analysis of GGT  
(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	10.0	1.07 (0.85,1.35)	0.574
	Medium	257	9.7		
	High	130	10.0		
b) Maximal (n=737)	Low	184	4.9	1.20 (1.00,1.43)	0.052
	Medium	368	9.5		
	High	185	9.7		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=514)	1.10 (0.86,1.41)***	0.437***	INIT*RACE (p=0.043) INIT*DC (p=0.006) ALC*IC (p=0.042)
d) Maximal (n=732)	1.24 (1.03,1.50)***	0.028***	INIT*DC (p=0.005) ALC*IC (p=0.012)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

\*\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (p≤0.01); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-17. (Continued)

Analysis of GGT  
(Discrete)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	5.6 (72)	11.1 (126)	7.5 (53)	1.11 (0.75,1.65)	0.728 <sup>b</sup> 0.599 <sup>c</sup>
	>18.6	12.1 (58)	9.9 (131)	11.7 (77)	1.02 (0.75,1.38)	0.908 <sup>c</sup>
f) Maximal (n=737)	≤18.6	4.8 (105)	6.9 (189)	11.0 (82)	1.27 (0.95,1.71)	0.522 <sup>b</sup> 0.108 <sup>c</sup>
	>18.6	5.1 (79)	11.2 (178)	10.6 (104)	1.13 (0.89,1.42)	0.320 <sup>c</sup>
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=514)	≤18.6	1.03 (0.68,1.57)		0.695 <sup>b</sup> 0.888 <sup>c</sup>	ALC (p<0.001) AGE*DC (p=0.044)	
	>18.6	0.93 (0.67,1.28)		0.656 <sup>c</sup>		
h) Maximal (n=732)	≤18.6	1.34 (0.99,1.81)		0.410 <sup>b</sup> 0.061 <sup>c</sup>	ALC*IC (p=0.019)	
	>18.6	1.14 (0.89,1.45)		0.308 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-17. (Continued)**

**Analysis of GGT  
(Discrete)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	6.0	All Categories		0.047
Unknown	341	5.6	Unknown vs. Background	0.92 (0.53,1.59)	0.763
Low	193	9.8	Low vs. Background	1.70 (0.97,2.97)	0.062
High	186	10.8	High vs. Background	1.88 (1.08,3.25)	0.025
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	777	All Categories		0.033**	DXCAT*DC (p=0.023) ALC*DRKYR (p=0.013)
Unknown	338	Unknown vs. Background	0.95 (0.54,1.65)**	0.844**	
Low	191	Low vs. Background	1.82 (1.03,3.22)**	0.039**	
High	182	High vs. Background	2.00 (1.13,3.56)**	0.018**	
Total	1,488				

\*\*Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

For both cohorts, the unadjusted and adjusted discrete analyses of GGT did not find a significant interaction between current dioxin and time since tour (Table 10-17 [e-h]:  $p > 0.40$  for each analysis). The adjusted maximal analysis revealed a marginally significant association between discretized GGT and current dioxin for Ranch Hands with a later tour (time  $\leq 18.6$ : Adj. RR=1.34,  $p=0.061$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis found that the prevalence of abnormally high levels of GGT differed significantly among categories (Table 10-17 [i]: 6.0%, 5.6%, 9.8%, and 10.8% for the background, unknown, low, and high current dioxin categories,  $p=0.047$ ). The estimated relative risk was marginally significant for the low versus background contrast (Est. RR=1.70, 95% C.I.: [0.97,2.97],  $p=0.062$ ) and significant for the high versus background contrast (Est. RR=1.88, 95% C.I.: [1.08,3.25],  $p=0.025$ ).

The adjusted analysis detected a significant interaction between current dioxin and degreasing chemical exposure (Table 10-17 [j]:  $p=0.023$ ). Stratified results found a significant difference among the percentages of abnormal levels of GGT for participants who had never been exposed to degreasing chemicals (Appendix Table I-1: 6.1%, 4.8%, 8.2%, and 24.4% for the background, unknown, low, and high current dioxin categories,  $p=0.002$ ). The adjusted relative risk for the high versus background contrast was highly significant (Adj. RR=5.89, 95% C.I.: [2.43,14.29],  $p<0.001$ ). By contrast, the prevalence of abnormal levels of GGT did not differ significantly among current dioxin categories for participants who had been exposed to degreasing chemicals (6.0%, 6.4%, 10.8%, and 6.4% for the background, unknown, low, and high current dioxin categories,  $p=0.305$ ). The low versus background contrast was marginally significant in this stratum (Adj. RR=1.93, 95% C.I.: [0.98,3.82],  $p=0.058$ ).

After excluding the interaction, the results of the adjusted analysis were similar to the unadjusted analysis, except that the low versus background contrast became significant (Table 10-17 [j]: Adj. RR=1.82, 95% C.I.: [1.03,3.22],  $p=0.039$ ). The overall contrast remained significant ( $p=0.033$ ), as did the high versus background contrast (Adj. RR=2.00, 95% C.I.: [1.13,3.56],  $p=0.018$ ).

### ***Alkaline Phosphatase (Continuous)***

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted analyses of alkaline phosphatase treated as a continuous variable did not show a significant association with initial dioxin for the minimal cohort (Table 10-18 [a]:  $p=0.380$ ), but the association with initial dioxin was significantly positive for the maximal cohort (Table 10-18 [b]:  $p=0.007$ ). The mean alkaline phosphatase increased from 87.81 U/L in the low initial dioxin category to 94.31 U/L in the high initial dioxin category. The mean for the medium initial dioxin category was 94.17 U/L.

The adjusted findings supported the unadjusted results. The association between alkaline phosphatase and initial dioxin was not significant for the adjusted minimal analysis (Table 10-18 [c]:  $p=0.554$ ), but the adjusted maximal analysis displayed a significant positive relationship (Table 10-18 [d]:  $p=0.030$ ).

**TABLE 10-18.**  
**Analysis of Alkaline Phosphatase (U/L)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Mean<sup>a</sup></b>	<b>Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>
a) Minimal (n=517) (R <sup>2</sup> =0.001)	Low	130	92.58	0.0072 (0.0081)	0.380
	Medium	257	94.55		
	High	130	94.44		
b) Maximal (n=737) (R <sup>2</sup> =0.010)	Low	184	87.81	0.0167 (0.0062)	0.007
	Medium	368	94.17		
	High	185	94.31		

  

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>						
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Adj. Mean<sup>a</sup></b>	<b>Adj. Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c) Minimal (n=513) (R <sup>2</sup> =0.020)	Low	130	90.98	0.0049 (0.0083)	0.554	WINE (p=0.079) RACE*IC (p=0.045)
	Medium	254	92.66			
	High	129	92.30			
d) Maximal (n=731) (R <sup>2</sup> =0.036)	Low	183	87.02	0.0138 (0.0063)	0.030	LWINE (p=0.004) RACE*IC (p=0.013)
	Medium	365	93.07			
	High	183	92.57			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm alkaline phosphatase versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-18. (Continued)**  
**Analysis of Alkaline Phosphatase (U/L)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.002)	≤18.6	91.49 (72)	94.6 (126)	93.68 (53)	0.0027 (0.0133)	0.715 <sup>c</sup> 0.838 <sup>d</sup>	
	>18.6	95.90 (58)	93.30 (131)	95.53 (77)	0.0090 (0.0109)	0.408 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.009)	≤18.6	87.62 (105)	93.47 (189)	93.12 (82)	0.0177 (0.0097)	0.704 <sup>c</sup> 0.069 <sup>d</sup>	
	>18.6	88.97 (79)	94.73 (178)	94.83 (104)	0.0128 (0.0085)	0.135 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=513) (R <sup>2</sup> =0.034)	≤18.6	89.96** (72)	92.34** (126)	91.56** (52)	0.0012 (0.0135)**	0.863*** 0.929***	CURR*TIME*LWINE (p=0.013) WINE (p=0.066)
	>18.6	95.05** (58)	91.51** (128)	93.12** (77)	0.0042 (0.0111)**	0.707***	RACE*IC (p=0.043)
h) Maximal (n=731) (R <sup>2</sup> =0.063)	≤18.6	87.09** (104)	92.18** (189)	92.20** (81)	0.0169 (0.0099)**	0.551*** 0.090***	CURR*TIME*RACE (p=0.045) CURR*TIME*WINE
	>18.6	88.30** (78)	94.09** (176)	93.25** (103)	0.0092 (0.0088)**	0.297***	(p=0.012) AGE (p=0.145) LWINE (p=0.034) RACE*IC (p=0.008)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm alkaline phosphatase versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-18. (Continued)**  
**Analysis of Alkaline Phosphatase (U/L)**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	90.28	All Categories		0.064
Unknown	341	91.94	Unknown vs. Background	1.66 --	0.245
Low	193	93.92	Low vs. Background	3.64 --	0.041
High	186	94.07	High vs. Background	3.79 --	0.036
Total	1,499		(R <sup>2</sup> =0.005)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	777	90.08	All Categories		0.098	AGE (p=0.039) CWINE (p=0.010)
Unknown	339	92.03	Unknown vs. Background	1.95 --	0.170	LWINE (p=0.049)
Low	191	93.29	Low vs. Background	3.21 --	0.070	IC (p<0.001)
High	184	93.58	High vs. Background	3.50 --	0.055	
Total	1,491		(R <sup>2</sup> =0.027)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>p-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the unadjusted analyses of current dioxin and time since tour did not detect a significant interaction between current dioxin and time for the continuous analysis of alkaline phosphatase (Table 10-18 [e] and [f]:  $p > 0.70$  for both cohorts). For the maximal cohort, the unadjusted association between alkaline phosphatase and current dioxin was of borderline significance for Ranch Hands with a later tour (time  $\leq 18.6$ :  $p = 0.069$ ). The mean levels of alkaline phosphatase for low, medium, and high current dioxin were 87.62, 93.47, and 93.12 U/L.

The adjusted minimal analysis detected a significant current dioxin-by-time-by-lifetime wine history interaction (Table 10-18 [g]:  $p = 0.013$ ). The lifetime wine history covariate was dichotomized to explore the interaction. Stratified results showed that the current dioxin-by-time interaction was not significant in either lifetime wine history stratum (Appendix Table I-1:  $p = 0.160$  for participants who had never drunk wine, and  $p = 0.141$  for participants who had drunk wine). After excluding the interaction with lifetime wine history, the current dioxin-by-time interaction was not significant for the adjusted minimal analysis (Table 10-18 [g]:  $p = 0.863$ ), supporting the unadjusted findings.

The adjusted maximal analysis found two significant current dioxin-by-time-by-covariate interactions (Table 10-18 [h]: current dioxin-by-time-by-race,  $p = 0.045$ ; current dioxin-by-time-by-current wine use,  $p = 0.012$ ). Separate analyses were done for Blacks and for non-Blacks to explore the interaction with current wine use. The current dioxin-by-time interaction was not significant for Blacks (Appendix Table I-1:  $p = 0.205$ ) after deleting the current dioxin-by-time-by-current wine use interaction, which was not significant ( $p = 0.769$ ). However, for non-Blacks, there was a significant current dioxin-by-time-by-current wine use interaction ( $p = 0.010$ ). Categorizing current wine use, the current dioxin-by-time interaction was not significant within either current wine use stratum ( $p = 0.486$  for non-Blacks who did not currently drink wine, and  $p = 0.288$  for non-Blacks who currently drink wine). After excluding the interactions with race and current wine use, the current dioxin-by-time interaction was not significant in the adjusted maximal analysis (Table 10-18 [h]:  $p = 0.551$ ). As in the unadjusted analysis, the association between current dioxin and alkaline phosphatase was marginally significant for Ranch Hands with a later tour (time  $\leq 18.6$ :  $p = 0.090$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

Both the unadjusted and adjusted categorized current dioxin analyses for alkaline phosphatase in its continuous form found a marginally significant overall difference among current dioxin categories (Table 10-18 [i] and [j]:  $p = 0.064$  and  $p = 0.098$ , respectively). The unadjusted mean levels of alkaline phosphatase were 90.28, 91.94, 93.92, and 94.07 U/L for the background, unknown, low, and high current dioxin categories. The corresponding adjusted means were 90.08, 92.02, 93.29, and 93.58 U/L. Unadjusted, the means for the low and high current dioxin categories were significantly more than the background mean ( $p = 0.041$  and  $p = 0.036$ , respectively). After covariate adjustment, the low versus background contrast ( $p = 0.070$ ) and the high versus background contrast ( $p = 0.055$ ) became marginally significant.



## **Alkaline Phosphatase (Discrete)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analysis did not show a significant relative risk of abnormally high alkaline phosphatase levels under the minimal assumption (Table 10-19 [a]:  $p=0.245$ ). However, under the maximal assumption, the estimated relative risk was marginally significant (Table 10-19 [b]: Est. RR=1.25,  $p=0.077$ ). For the maximal cohort, the percentage of abnormal alkaline phosphatase values increased from 2.2 percent in the low current dioxin category to 4.9 percent for both the medium and high current dioxin categories.

The adjusted initial dioxin analyses for discretized alkaline phosphatase did not find a significant relative risk for either the minimal (Table 10-19 [c]:  $p=0.363$ ) or maximal (Table 10-19 [d]:  $p=0.179$ ) cohort. The maximal analysis was adjusted for lifetime wine history and the interaction between current wine use and industrial chemical exposure.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

For both cohorts, the interaction between current dioxin and time since tour was not significant in either the unadjusted or the adjusted analyses of discretized alkaline phosphatase (Table 10-19 [e-h]:  $p>0.25$  for each analysis). However, under the maximal assumption, there was a significant increased risk of abnormally high alkaline phosphatase levels for Ranch Hands with an early tour (time>18.6: Est. RR=1.35,  $p=0.046$ ). The percentages of abnormally high alkaline phosphatase levels were 1.3, 5.1, and 7.7 percent for the low, medium, and high current dioxin categories.

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

Both the unadjusted and adjusted categorized current dioxin analyses did not find a significant difference in the prevalence of abnormally high levels of alkaline phosphatase among current dioxin categories (Table 10-19 [i] and [j]:  $p>0.45$  for all contrasts).

## **D-Glucaric Acid (Continuous)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

In the unadjusted analyses, the association between initial dioxin and d-glucaric acid in its continuous form was not significant for the minimal cohort (Table 10-20 [a]:  $p=0.377$ ), but the association was marginally positive for the maximal cohort (Table 10-20 [b]:  $p=0.065$ ). The mean levels of d-glucaric acid were 12.79, 14.92, and 15.86  $\mu\text{M}$  for the low, medium, and high initial dioxin categories in the maximal cohort. After adjustment for lifetime alcohol history and the age-by-current alcohol use interaction, the association became nonsignificant for the maximal cohort (Table 10-20 [d]:  $p=0.270$ ).

The adjusted analysis for the minimal cohort detected a significant initial dioxin-by-race interaction (Table 10-20 [c]:  $p=0.044$ ). Stratified results showed a marginally significant negative association between initial dioxin and d-glucaric acid for Blacks (Appendix Table I-1:  $p=0.061$ ; Adj. means: 26.89, 13.82, and 8.67  $\mu\text{M}$  for the low, medium, and high initial dioxin categories) that contrasted with a nonsignificant positive association for non-Blacks ( $p=0.340$ ). After excluding the interaction, the adjusted minimal analysis was not significant (Table 10-20 [c]:  $p=0.580$ ).

**TABLE 10-19.**  
**Analysis of Alkaline Phosphatase**  
**(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	3.1	1.21 (0.89,1.64)	0.245
	Medium	257	5.4		
	High	130	5.4		
b) Maximal (n=737)	Low	184	2.2	1.25 (0.98,1.59)	0.077
	Medium	368	4.9		
	High	185	4.9		
Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
c) Minimal (n=512)	1.16 (0.85,1.58)		0.363	LWINE (p=0.121)	
d) Maximal (n=731)	1.19 (0.93,1.52)		0.179	LWINE (p=0.111) WINE*IC (p=0.044)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-19. (Continued)**  
**Analysis of Alkaline Phosphatase**  
**(Discrete)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	2.8 (72)	4.8 (126)	1.9 (53)	0.91 (0.48,1.75)	0.377 <sup>b</sup> 0.787 <sup>c</sup>
	>18.6	6.9 (58)	4.6 (131)	7.8 (77)	1.27 (0.88,1.83)	0.200 <sup>c</sup>
f) Maximal (n=737)	≤18.6	2.9 (105)	4.2 (189)	2.4 (82)	1.01 (0.65,1.58)	0.281 <sup>b</sup> 0.952 <sup>c</sup>
	>18.6	1.3 (79)	5.1 (178)	7.7 (104)	1.35 (1.01,1.83)	0.046 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=512)	≤18.6	0.88 (0.46,1.71)		0.407 <sup>b</sup> 0.715 <sup>c</sup>	LWINE (p=0.118)	
	>18.6	1.21 (0.83,1.75)		0.318 <sup>c</sup>		
h) Maximal (n=737)	≤18.6	1.01 (0.65,1.58)		0.281 <sup>b</sup> 0.952 <sup>c</sup>	--	
	>18.6	1.35 (1.01,1.83)		0.046 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-19. (Continued)**  
**Analysis of Alkaline Phosphatase**  
**(Discrete)**

<b>i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted</b>					
Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	4.7	All Categories		0.851
Unknown	341	3.8	Unknown vs. Background	0.79 (0.42,1.52)	0.485
Low	193	4.7	Low vs. Background	0.98 (0.47,2.07)	0.960
High	186	5.4	High vs. Background	1.14 (0.56,2.34)	0.721
Total	1,499				

  

<b>j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted</b>					
Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	777	All Categories		0.950	AGE (p=0.056)
Unknown	339	Unknown vs. Background	0.88 (0.46,1.69)	0.694	RACE (p=0.039)
Low	191	Low vs. Background	0.91 (0.43,1.94)	0.809	LWINE*IC (p<0.001)
High	183	High vs. Background	1.11 (0.53,2.32)	0.777	
Total	1,490				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 10-20.

**Analysis of D-Glucaric Acid ( $\mu\text{M}$ )  
(Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=503) (R <sup>2</sup> =0.002)	Low	124	15.78	0.0585 (0.0662)	0.377
	Medium	252	14.75		
	High	127	15.54		
b) Maximal (n=714) (R <sup>2</sup> =0.005)	Low	176	12.79	0.0907 (0.0492)	0.065
	Medium	357	14.92		
	High	181	15.86		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=503) (R <sup>2</sup> =0.018)	Low	124	17.20**	0.0379 (0.0684)**	0.580**	INIT*RACE (p=0.044) AGE (p=0.147)
	Medium	252	15.92**			
	High	127	16.37**			
d) Maximal (n=684) (R <sup>2</sup> =0.028)	Low	170	12.76	0.0564 (0.0511)	0.270	DRKYR85 (p=0.108) AGE*ALC85 (p=0.007)
	Medium	341	14.77			
	High	173	15.13			

<sup>a</sup>Transformed from square root scale.

<sup>b</sup>Slope and standard error based on square root d-glucaric acid versus log<sub>2</sub> dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

DRKYR85 and ALC85 refer to lifetime alcohol history and current alcohol use, based on information from the 1985 examination.

**TABLE 10-20. (Continued)**  
**Analysis of D-Glucaric Acid ( $\mu\text{M}$ )**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=503) (R <sup>2</sup> =0.002)	≤18.6	14.76 (68)	15.75 (124)	14.74 (51)	0.0462 (0.1095)	0.846 <sup>c</sup> 0.673 <sup>d</sup>	
	>18.6	15.18 (56)	15.06 (128)	15.29 (76)	0.0735 (0.0875)	0.402 <sup>d</sup>	
f) Maximal (n=714) (R <sup>2</sup> =0.004)	≤18.6	13.14 (100)	14.61 (182)	16.32 (80)	0.0900 (0.0773)	0.993 <sup>c</sup> 0.245 <sup>d</sup>	
	>18.6	12.84 (76)	15.03 (174)	15.48 (102)	0.0890 (0.0670)	0.185 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=503) (R <sup>2</sup> =0.008)	≤18.6	15.06 (68)	15.54 (124)	13.87 (51)	0.0001 (0.1124)	0.792 <sup>c</sup> 0.999 <sup>d</sup>	AGE (p=0.084)
	>18.6	15.93 (56)	15.26 (128)	15.07 (76)	0.0371 (0.0898)	0.680 <sup>d</sup>	
h) Maximal (n=684) (R <sup>2</sup> =0.027)	≤18.6	12.96 (97)	14.42 (175)	14.84 (75)	0.0447 (0.0801)	0.984 <sup>c</sup> 0.577 <sup>d</sup>	DRKYR85 (p=0.102) AGE*ALC85 (p=0.008)
	>18.6	13.23 (74)	15.27 (165)	14.57 (98)	0.0426 (0.0694)	0.540 <sup>d</sup>	

<sup>a</sup>Transformed from square root scale.

<sup>b</sup>Slope and standard error based on square root d-glucaric acid versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-20. (Continued)**  
**Analysis of D-Glucaric Acid ( $\mu\text{M}$ )**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	746	14.14	All Categories		0.504
Unknown	328	14.09	Unknown vs. Background	-0.05 --	0.953
Low	190	14.62	Low vs. Background	0.48 --	0.672
High	182	15.85	High vs. Background	1.71 --	0.147
Total	1,446		(R <sup>2</sup> =0.002)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	727	14.11	All Categories		0.781	DRKYR85 (p=0.100) RACE*IC85 (p=0.003)
Unknown	317	13.99	Unknown vs. Background	-0.12 --	0.894	
Low	180	14.43	Low vs. Background	0.32 --	0.778	
High	173	15.22	High vs. Background	1.11 --	0.339	
Total	1,397		(R <sup>2</sup> =0.013)			

<sup>a</sup>Transformed from square root scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on square root scale.

<sup>f</sup>P-value is based on difference of means on square root scale.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.

Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

IC85 refers to degreasing chemical exposure based on information from the 1985 examination.

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Both the unadjusted and adjusted current dioxin and time since tour analyses of d-glucaric acid did not find a significant interaction between current dioxin and time (Table 10-20 [c]:  $p > 0.75$  for analyses under the minimal and maximal assumptions).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The mean levels of d-glucaric acid did not differ significantly among the current dioxin categories in either the unadjusted (Table 10-20 [i]:  $p = 0.504$ ) or adjusted (Table 10-20 [j]:  $p = 0.781$ ) categorized current dioxin analyses.

**D-Glucaric Acid (Discrete)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

There were only two abnormally high levels of d-glucaric acid in the minimal cohort and four in the maximal cohort. All were in either the low or medium current dioxin category. The unadjusted initial dioxin analyses were not significant for both cohorts (Table 10-21 [a] and [b]:  $p = 0.631$  and  $p = 0.430$  for the minimal and maximal cohorts). No adjusted analyses were done because of the sparseness of the data.

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The current dioxin-by-time since tour interaction was not analyzed under the minimal assumption because there was only one abnormally high level of d-glucaric acid within each time stratum. Under the maximal assumption, the interaction was not significant in the unadjusted analysis (Table 10-21 [c]:  $p = 0.394$ ). No adjusted analyses were done due to sparse data.

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis did not find a significant overall difference in the prevalences of abnormally high levels of d-glucaric acid (Table 10-21 [e]: 0.4%, 1.5%, 0.0%, and 0.5% for the background, unknown, low, and high categories,  $p = 0.107$ ). No adjusted analysis was done because there were so few abnormalities.

**Total Bilirubin (Continuous)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analyses did not find a significant association with total bilirubin for both the minimal (Table 10-22 [a]:  $p = 0.934$ ) and maximal (Table 10-22 [b]:  $p = 0.828$ ) cohorts. The adjusted minimal analysis was identical to the unadjusted analysis because no covariates were associated with total bilirubin. The adjusted maximal analysis detected a significant initial dioxin-by-race interaction (Table 10-22 [d]:  $p = 0.031$ ). Stratified results showed a significant negative association between total bilirubin and initial dioxin for Blacks (Appendix Table I-1:  $p = 0.031$ ). The adjusted mean levels of total bilirubin decreased with levels of initial dioxin (1.212, 0.803, and 0.732 mg/dl, for the low, medium, and high initial dioxin categories). The association for non-Blacks was positive, but not significant ( $p = 0.885$ ). After excluding the interaction, the adjusted maximal analysis was not significant (Table 10-22 [d]:  $p = 0.840$ ).



**TABLE 10-21.**  
**Analysis of D-Glucaric Acid**  
**(Discrete)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Abnormal High</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=503)	Low	124	0.8	0.73 (0.18,2.88)	0.631
	Medium	252	0.4		
	High	127	0.0		
b) Maximal (n=714)	Low	176	0.6	0.72 (0.30,1.71)	0.430
	Medium	357	0.8		
	High	181	0.0		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-21. (Continued)**

**Analysis of D-Glucaric Acid  
(Discrete)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
<b>Assumption</b>	<b>Time (Yrs.)</b>	<b>Percent Abnormal High/(n) Current Dioxin</b>			<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
		<b>Low</b>	<b>Medium</b>	<b>High</b>		
c) Minimal (n=503)	≤18.6	0.0	0.8	0.0	--	--
		(68)	(124)	(51)		
	>18.6	1.8	0.0	0.0	--	--
		(56)	(128)	(76)		
d) Maximal (n=714)	≤18.6	1.0	0.0	1.3	0.93 (0.29,3.00)	0.394 <sup>b</sup>
		(100)	(182)	(80)		0.899 <sup>c</sup>
	>18.6	1.3	0.6	0.0	0.39 (0.07,2.27)	0.292 <sup>c</sup>
		(76)	(174)	(102)		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-21. (Continued)**

**Analysis of D-Glucaric Acid  
(Discrete)**

**e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	746	0.4	All Categories		0.106
Unknown	328	1.5	Unknown vs. Background	3.83 (0.91,16.14)	0.067
Low	190	0.0	Low vs. Background	—	—
High	182	0.5	High vs. Background	1.37 (0.14,13.23)	0.787
Total	1,446				

--: Relative risk, confidence interval, and p-value not given due to absence of abnormalities.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.

Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.

Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .

High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

**TABLE 10-22.**  
**Analysis of Total Bilirubin (mg/dl)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> <0.001)	Low	130	0.814	-0.0009 (0.0111)	0.934
	Medium	257	0.768		
	High	130	0.784		
b) Maximal (n=737) (R <sup>2</sup> <0.001)	Low	184	0.788	-0.0018 (0.0081)	0.828
	Medium	368	0.777		
	High	185	0.784		

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=517) (R <sup>2</sup> <0.001)	Low	130	0.814	-0.0009 (0.0111)	0.934	--
	Medium	257	0.768			
	High	130	0.784			
d) Maximal (n=737) (R <sup>2</sup> =0.008)	Low	184	0.812**	-0.0016 (0.0081)**	0.840**	INIT*RACE (p=0.031)
	Medium	368	0.798**			
	High	185	0.806**			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm total bilirubin versus log<sub>2</sub> dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-22. (Continued)**  
**Analysis of Total Bilirubin (mg/dl)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517) (R <sup>2</sup> <0.001)	≤18.6	0.796 (72)	0.789 (126)	0.772 (53)	-0.0068 (0.0181)	0.607 <sup>c</sup> 0.707 <sup>d</sup>
	>18.6	0.779 (58)	0.771 (131)	0.794 (77)	0.0052 (0.0148)	0.724 <sup>d</sup>
f) Maximal (n=737) (R <sup>2</sup> =0.002)	≤18.6	0.812 (105)	0.772 (189)	0.798 (82)	-0.0082 (0.0126)	0.346 <sup>c</sup> 0.516 <sup>d</sup>
	>18.6	0.766 (79)	0.778 (178)	0.777 (104)	0.0076 (0.0111)	0.491 <sup>d</sup>

**Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted**

Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=517) (R <sup>2</sup> <0.001)	≤18.6	0.796 (72)	0.789 (126)	0.772 (53)	-0.0068 (0.0181)	0.607 <sup>c</sup> 0.707 <sup>d</sup>	--
	>18.6	0.779 (58)	0.771 (131)	0.794 (77)	0.0052 (0.0148)	0.724 <sup>d</sup>	
h) Maximal (n=737) (R <sup>2</sup> =0.002)	≤18.6	0.812 (105)	0.772 (189)	0.798 (82)	-0.0082 (0.0126)	0.346 <sup>c</sup> 0.516 <sup>d</sup>	--
	>18.6	0.766 (79)	0.778 (178)	0.777 (104)	0.0076 (0.0111)	0.491 <sup>d</sup>	

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm total bilirubin versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-22. (Continued)**  
**Analysis of Total Bilirubin (mg/dl)**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	0.793	All Categories		0.466
Unknown	341	0.773	Unknown vs. Background	-0.020 --	0.191
Low	193	0.770	Low vs. Background	-0.023 --	0.229
High	186	0.786	High vs. Background	-0.007 --	0.715
Total	1,499		(R <sup>2</sup> =0.002)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	779	0.779	All Categories		0.409	ALC (p=0.116) AGE*RACE (p=0.023)
Unknown	339	0.755	Unknown vs. Background	-0.024 --	0.121	AGE*IC (p=0.008)
Low	191	0.760	Low vs. Background	-0.019 --	0.332	AGE*DC (p=0.040)
High	185	0.776	High vs. Background	-0.003 --	0.904	
Total	1,494		(R <sup>2</sup> =0.016)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The unadjusted current dioxin and time since tour analyses for total bilirubin did not find a significant interaction between current dioxin and time for both the minimal (Table 10-22 [e]:  $p=0.607$ ) and maximal (Table 10-22 [f]:  $p=0.346$ ) analyses. The adjusted analyses were identical to the unadjusted analyses because no covariates were retained in the final models.

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The mean levels of total bilirubin did not differ significantly among the four current dioxin categories for either the unadjusted or adjusted analysis (Table 10-22 [i] and [j]:  $p=0.466$  and  $p=0.409$ ).

**Total Bilirubin (Discrete)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analyses of discretized total bilirubin found that the relative risk of abnormally high total bilirubin levels was significantly less than 1 for both the minimal (Table 10-23 [a]: Est. RR=0.46,  $p=0.007$ ) and maximal (Table 10-23 [b]: Est. RR=0.68,  $p=0.033$ ) cohorts. The percentage of abnormally high total bilirubin values decreased with initial dioxin for the minimal cohort (5.4%, 3.1%, and 0.0% for the low, medium, and high initial dioxin categories). The corresponding percentages for the maximal cohort categories were 2.7, 4.3, and 0.5 percent.

The relative risk remained significantly less than 1 for each cohort after covariate adjustment (Table 10-23 [c] and [d]: Adj. RR=0.37,  $p=0.001$  for the minimal cohort; Adj. RR=0.63,  $p=0.014$  for the maximal cohort).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the association between discretized total bilirubin and current dioxin did not differ significantly between time since tour strata for either the unadjusted or adjusted analyses (Table 10-23 [e-h]:  $p>0.20$  for each analysis). Both the unadjusted and adjusted analyses for the minimal cohort found that the prevalence of abnormally high total bilirubin levels significantly decreased with current dioxin for Ranch Hands with an early tour (time>18.6: Est. RR=0.34,  $p=0.045$ ; Adj. RR=0.18,  $p=0.008$ ). For these Ranch Hands, the percentages of abnormally high total bilirubin levels for the low, medium, and high current dioxin categories were 5.2, 3.8, and 0.0 percent. For the maximal cohort, the adjusted association between discretized total bilirubin and current dioxin was of borderline significance for Ranch Hands with an early tour (Adj. RR=0.60,  $p=0.076$ ).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis displayed a significant overall difference among the percentages of abnormally high levels of total bilirubin (Table 10-23 [i]: 3.9%, 3.2%, 4.1%, and 0.5% for the background, unknown, low, and high current dioxin categories,  $p=0.048$ ). The prevalence rate in the high current dioxin category was significantly less than the prevalence rate in the background category (Est. RR=0.13, 95% C.I.: [0.02,1.00],  $p=0.050$ ).

**TABLE 10-23.**  
**Analysis of Total Bilirubin**  
**(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	5.4	0.46 (0.24,0.89)	0.007
	Medium	257	3.1		
	High	130	0.0		
b) Maximal (n=737)	Low	184	2.7	0.68 (0.46,1.00)	0.033
	Medium	368	4.3		
	High	185	0.5		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=511)	0.37 (0.18,0.77)	0.001	AGE (p=0.070) ALC (p=0.113) IC (p=0.040) DRKYR*DC (p=0.023)
d) Maximal (n=728)	0.63 (0.42,0.94)	0.014	ALC*IC (p=0.041) DRKYR*DC (p=0.012)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.  
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.



TABLE 10-23. (Continued)

**Analysis of Total Bilirubin  
(Discrete)**

**Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted**

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	2.8	4.0	0.0	0.55 (0.21,1.43)	0.517 <sup>b</sup> 0.221 <sup>c</sup>
		(72)	(126)	(53)		
	>18.6	5.2 (58)	3.8 (131)	0.0 (77)	0.34 (0.12,0.98)	0.045 <sup>c</sup>
f) Maximal (n=737)	≤18.6	3.8	3.7	1.2	0.64 (0.35,1.16)	0.820 <sup>b</sup> 0.141 <sup>c</sup>
		(105)	(189)	(82)		
	>18.6	1.3 (79)	5.1 (178)	0.0 (104)	0.70 (0.41,1.21)	0.204 <sup>c</sup>

**Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted**

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=511)	≤18.6	0.48 (0.17,1.34)	0.227 <sup>b</sup>	AGE (p=0.019) DRKYR (p=0.109) IC (p=0.019) DC (p=0.019)
			0.159 <sup>c</sup>	
	>18.6	0.18 (0.05,0.64)	0.008 <sup>c</sup>	
h) Maximal (n=728)	≤18.6	0.62 (0.33,1.17)	0.934 <sup>b</sup>	ALC*IC (p=0.044) DRKYR*DC (p=0.015)
			0.139 <sup>c</sup>	
	>18.6	0.60 (0.34,1.06)	0.076 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-23. (Continued)**

**Analysis of Total Bilirubin  
(Discrete)**

<b>i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted</b>					
Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	3.9	All Categories		0.048
Unknown	341	3.2	Unknown vs. Background	0.83 (0.41,1.68)	0.609
Low	193	4.1	Low vs. Background	1.08 (0.49,2.39)	0.850
High	186	0.5	High vs. Background	0.13 (0.02,1.00)	0.050
Total	1,499				
<b>j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted</b>					
Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.018	AGE (p=0.004) RACE*ALC (p=0.030) IC*DC (p=0.047)
Unknown	339	Unknown vs. Background	0.77 (0.37,1.61)	0.486	
Low	191	Low vs. Background	1.05 (0.47,2.36)	0.900	
High	185	High vs. Background	0.11 (0.01,0.81)	0.030	
Total	1,494				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

The adjusted results paralleled the unadjusted findings. The overall contrast was significant (Table 10-23 [j]:  $p=0.018$ ) and the high versus background relative risk was significantly less than 1 (Adj. RR=0.11, 95% C.I.: [0.01,0.81],  $p=0.030$ ).

#### **Direct Bilirubin (Continuous)**

##### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under the minimal assumption, the unadjusted initial dioxin analysis was not significant for direct bilirubin (Table 10-24 [a]:  $p=0.522$ ), but the association between initial dioxin and direct bilirubin was marginally significant under the maximal assumption (Table 10-24 [b]:  $p=0.097$ ). The unadjusted mean levels of direct bilirubin for the maximal cohort were 0.142, 0.158, and 0.170 mg/dl for the low, medium, and high initial dioxin categories.

After covariate adjustment, the association between initial dioxin and direct bilirubin remained nonsignificant under the minimal assumption (Table 10-24 [c]:  $p=0.317$ ), but the association became significant for the maximal assumption (Table 10-24 [d]:  $p=0.038$ ). The maximal analysis was adjusted for current alcohol use, degreasing chemical exposure, and the race-by-industrial chemical exposure interaction. Adjusted mean levels of direct bilirubin increased with initial dioxin (0.161, 0.178, and 0.195 mg/dl for the low, medium, and high maximal initial dioxin categories).

##### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not significant for either the unadjusted or adjusted analyses (Table 10-24 [e-h]:  $p>0.60$  for each analysis).

##### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted analysis of categorized current dioxin found that the mean direct bilirubin for the high current dioxin category was significantly more than the background mean (Table 10-24 [i]: 0.171 mg/dl versus 0.149 mg/dl,  $p=0.025$ ), although the overall category contrast was not significant ( $p=0.120$ ). The mean levels of direct bilirubin for the unknown and low categories were 0.148 mg/dl and 0.157 mg/dl.

The adjusted analysis detected a significant interaction between categorized current dioxin and race (Table 10-24 [j]:  $p=0.006$ ). Stratified results showed that the mean levels of direct bilirubin differed significantly among current dioxin categories for Blacks (Appendix Table I-1: 0.119, 0.261, 0.162, and 0.175 mg/dl for the background, unknown, low, and high current dioxin categories,  $p=0.008$ ) and that the overall difference among categories was marginally significant for non-Blacks (0.153, 0.145, 0.159, and 0.175 mg/dl for the background, unknown, low, and high current dioxin categories,  $p=0.061$ ). For Blacks, the mean direct bilirubin in the unknown category was significantly more than the background mean ( $p<0.001$ ). For non-Blacks, the mean for the high current dioxin category was significantly more than the background mean ( $p=0.033$ ). The interaction occurred because the unknown current dioxin category had the largest mean for Blacks, but it had the smallest mean of the four current dioxin categories for non-Blacks. After deleting the interaction, the overall difference in adjusted mean levels of direct bilirubin among current dioxin categories was marginally significant (Table 10-24 [j]: 0.148, 0.146, 0.156, and 0.172 mg/dl for the

**TABLE 10-24.**  
**Analysis of Direct Bilirubin (mg/dl)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> <0.001)	Low	130	0.169	0.0105 (0.0164)	0.522
	Medium	257	0.157		
	High	130	0.165		
b) Maximal (n=737) (R <sup>2</sup> =0.004)	Low	184	0.142	0.0200 (0.0120)	0.097
	Medium	368	0.158		
	High	185	0.170		

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=517) (R <sup>2</sup> =0.012)	Low	130	0.171	0.0165 (0.0165)	0.317	DC (p=0.015)
	Medium	257	0.161			
	High	130	0.173			
d) Maximal (n=732) (R <sup>2</sup> =0.027)	Low	183	0.161	0.0255 (0.0123)	0.038	ALC (p=0.094) DC (p=0.034) RACE*IC (p=0.038)
	Medium	365	0.178			
	High	184	0.195			

<sup>a</sup>Transformed from natural logarithm (X + 0.1) scale.

<sup>b</sup>Slope and standard error based on natural logarithm (direct bilirubin + 0.1) versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-24. (Continued)**  
**Analysis of Direct Bilirubin (mg/dl)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.001)	≤18.6	0.158 (72)	0.160 (126)	0.167 (53)	0.0042 (0.0268)	0.760 <sup>c</sup> 0.876 <sup>d</sup>	
	>18.6	0.159 (58)	0.162 (131)	0.168 (77)	0.0148 (0.0218)	0.500 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.004)	≤18.6	0.145 (105)	0.150 (189)	0.183 (82)	0.0183 (0.0189)	0.915 <sup>c</sup> 0.331 <sup>d</sup>	
	>18.6	0.146 (79)	0.162 (178)	0.163 (104)	0.0210 (0.0165)	0.205 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=517) (R <sup>2</sup> =0.035)	≤18.6	0.167 (72)	0.173 (126)	0.183 (53)	0.0103 (0.0277)	0.646 <sup>c</sup> 0.710 <sup>d</sup>	DC (p=0.013) AGE*ALC (p=0.049) RACE*IC (p=0.033)
	>18.6	0.163 (58)	0.174 (131)	0.187 (77)	0.0261 (0.0227)	0.251 <sup>d</sup>	
h) Maximal (n=732) (R <sup>2</sup> =0.026)	≤18.6	0.163 (105)	0.171 (188)	0.210 (81)	0.0258 (0.0190)	0.982 <sup>c</sup> 0.176 <sup>d</sup>	ALC (p=0.095) DC (p=0.035) RACE*IC (p=0.039)
	>18.6	0.167 (78)	0.183 (176)	0.187 (104)	0.0252 (0.0167)	0.131 <sup>d</sup>	

<sup>a</sup>Transformed from natural logarithm (X + 0.1) scale.

<sup>b</sup>Slope and standard error based on natural logarithm (direct bilirubin + 0.1) versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-24. (Continued)**  
**Analysis of Direct Bilirubin (mg/dl)**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	0.149	All Categories		0.120
Unknown	341	0.148	Unknown vs. Background	-0.001 --	0.846
Low	193	0.157	Low vs. Background	0.008 --	0.444
High	186	0.171	High vs. Background	0.022 --	0.025
Total	1,499		(R <sup>2</sup> =0.004)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	779	0.148***	All Categories		0.079***	DXCAT*RACE (p=0.006)
Unknown	341	0.146***	Unknown vs. Background	-0.002 -- ***	0.708***	AGE*DC (p=0.027)
Low	193	0.156***	Low vs. Background	0.008 -- ***	0.400***	AGE*IC (p=0.014)
High	186	0.172***	High vs. Background	0.024 -- ***	0.018***	
Total	1,499		(R <sup>2</sup> =0.020)			

<sup>a</sup>Transformed from natural logarithm (X + 0.1) scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm (X + 0.1) scale.

<sup>f</sup>p-value is based on difference of means on natural logarithm (X + 0.1) scale.

\*\*\*Categorized current dioxin-by-covariate interaction (p≤0.01); adjusted mean and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.  
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

background, unknown, low, and high current dioxin categories,  $p=0.079$ ). Comparable to the unadjusted analysis, the high current dioxin category mean was significantly more than the background mean ( $p=0.018$ ).

### **Direct Bilirubin (Discrete)**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analyses for direct bilirubin in its discrete form found that the relative risk of an abnormally high level of direct bilirubin was marginally less than 1 under the minimal assumption (Table 10-25 [a]: Est. RR=0.68,  $p=0.064$ ). The percentages of abnormal levels of direct bilirubin decreased with initial dioxin for the minimal cohort (7.7%, 3.5%, and 1.5% for the low, medium, and high initial dioxin categories). The relative risk was less than 1, but not significant, under the maximal assumption (Table 10-25 [b]: Est. RR=0.90,  $p=0.473$ ).

Under both the minimal and maximal assumptions, the adjusted analyses detected a significant initial dioxin-by-industrial chemical exposure interaction (Table 10-25 [c] and [d]:  $p=0.014$  and  $p=0.019$ , respectively). Appendix Table I-1 presents stratified results. Under the minimal assumption, the adjusted relative risk was significantly less than 1 for Ranch Hands who had been exposed to industrial chemicals (Adj. RR=0.42,  $p=0.018$ ; % abnormal: 12.3%, 2.7%, and 1.1% for the low, medium, and high initial dioxin categories). Under the maximal assumption, the adjusted relative risk was marginally less than 1 for these Ranch Hands (Adj. RR=0.68,  $p=0.081$ ; % abnormal: 2.3%, 6.1%, and 1.6% for the low, medium, and high initial dioxin categories). Under both assumptions, the adjusted relative risk was greater than 1, but not significant, for Ranch Hands who had never been exposed to industrial chemicals. After excluding the interaction, the adjusted relative risks were not significant for both cohorts (Table 10-25 [c]: Adj. RR=0.73,  $p=0.137$  for the minimal cohort; Table 10-25 [d]: Adj. RR=0.92,  $p=0.579$  for the maximal cohort).

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the unadjusted current dioxin and time since tour analyses for discretized direct bilirubin did not find a significant interaction between current dioxin and time (Table 10-25 [e] and [f]:  $p=0.961$  and  $p=0.893$  for the minimal and maximal cohorts). The current dioxin-by-time interaction also was not significant in the adjusted maximal analysis (Table 10-25 [h]:  $p=0.656$ ), but the adjusted minimal analysis detected a significant current dioxin-by-time-by-degreasing chemical exposure interaction (Table 10-25 [g]:  $p=0.040$ ). Stratified results showed a marginally significant interaction between current dioxin and time for Ranch Hands who had been exposed to degreasing chemicals (Appendix Table I-1:  $p=0.095$ ), although the association between current dioxin and direct bilirubin was not significant within either time stratum (time $\leq$ 18.6: Adj. RR=0.86,  $p=0.722$ ; time $>$ 18.6: Adj. RR=0.15,  $p=0.116$ ). The current dioxin-by-time interaction was not significant for Ranch Hands who had never been exposed to degreasing chemicals ( $p=0.232$ ). After excluding the current dioxin-by-time-by-degreasing chemical interaction, the adjusted minimal analysis did not find a significant interaction between current dioxin and time (Table 10-25 [g]:  $p=0.980$ ).

**TABLE 10-25.**  
**Analysis of Direct Bilirubin**  
**(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	7.7	0.68 (0.43,1.06)	0.064
	Medium	257	3.5		
	High	130	1.5		
b) Maximal (n=737)	Low	184	2.2	0.90 (0.66,1.21)	0.473
	Medium	368	4.6		
	High	185	2.7		
Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
c) Minimal (n=517)	0.73 (0.47,1.14)**		0.137**	INIT*IC (p=0.014) DC (p=0.008)	
d) Maximal (n=737)	0.92 (0.68,1.25)**		0.579**	INIT*IC (p=0.019) DC (p=0.003)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.



TABLE 10-25. (Continued)

Analysis of Direct Bilirubin  
(Discrete)Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	6.9 (72)	4.0 (126)	1.9 (53)	0.67 (0.34,1.33)	0.961 <sup>b</sup> 0.255 <sup>c</sup>
	>18.6	5.2 (58)	4.6 (131)	1.3 (77)	0.69 (0.37,1.27)	0.233 <sup>c</sup>
f) Maximal (n=737)	≤18.6	1.9 (105)	4.2 (189)	4.9 (82)	0.93 (0.59,1.45)	0.893 <sup>b</sup> 0.748 <sup>c</sup>
	>18.6	2.5 (79)	5.1 (178)	1.0 (104)	0.89 (0.58,1.37)	0.595 <sup>c</sup>

Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=517)	≤18.6	0.74 (0.37,1.47)**	0.980** <sup>b</sup> 0.388** <sup>c</sup>	CURR*TIME*DC (p=0.040)
	>18.6	0.75 (0.41,1.38)**	0.351** <sup>c</sup>	
h) Maximal (n=737)	≤18.6	1.02 (0.64,1.61)	0.656 <sup>b</sup> 0.936 <sup>c</sup>	RACE (p=0.102) IC (p=0.052) DC (p=0.003)
	>18.6	0.88 (0.56,1.39)	0.586 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).<sup>\*\*</sup>Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-25. (Continued)****Analysis of Direct Bilirubin  
(Discrete)****i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	3.9	All Categories		0.500
Unknown	341	2.3	Unknown vs. Background	0.60 (0.27,1.32)	0.205
Low	193	4.1	Low vs. Background	1.08 (0.49,2.39)	0.850
High	186	2.7	High vs. Background	0.69 (0.26,1.80)	0.448
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.461	AGE*DC (p=0.039)
Unknown	341	Unknown vs. Background	0.61 (0.28,1.35)	0.224	
Low	193	Low vs. Background	1.06 (0.47,2.36)	0.891	
High	186	High vs. Background	0.61 (0.23,1.61)	0.317	
Total	1,499				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

Both the unadjusted and adjusted categorized current dioxin analyses did not find a significant difference in the prevalence of abnormally high direct bilirubin levels among the four current dioxin categories (Table 10-25 [i] and [j]:  $p > 0.20$  for all contrasts).

**LDH (Continuous)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

For both cohorts, the unadjusted and adjusted analyses did not show a significant association between LDH and initial dioxin (Table 10-26 [a-d]:  $p > 0.50$  for all analyses).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not significant for either the unadjusted or adjusted analyses of LDH (Table 10-26 [e-h]:  $p > 0.25$  for each analysis).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The mean levels of LDH did not differ significantly among the four current dioxin categories for both the unadjusted (Table 10-26 [i]:  $p = 0.751$ ) and adjusted (Table 10-26 [j]:  $p = 0.725$ ) analyses.

**LDH (Discrete)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

There were only two abnormally high levels of LDH in the minimal cohort and five for the maximal cohort. The unadjusted initial dioxin analysis was not significant under the minimal assumption (Table 10-27 [a]:  $p = 0.470$ ), but the estimated relative risk of an abnormal level of LDH was marginally less than 1 under the maximal assumption (Table 10-27 [b]: Est. RR=0.47,  $p = 0.083$ ). No adjusted analyses were done because there were so few abnormalities.

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not evaluated because only one Ranch Hand with an early tour had an abnormal level of LDH. Also, only one Ranch Hand with a later tour had an abnormality under the minimal assumption. The association between current dioxin and discretized LDH was not significant for Ranch Hands with a later tour in the unadjusted maximal analysis (Table 10-27 [d]:  $p = 0.116$ ). No adjusted analyses were done because the abnormal data were sparse.

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The prevalence of abnormally high levels did not differ significantly among current dioxin categories for the unadjusted analysis (Table 10-27 [e]: 1.5%, 1.5%, 0.0%, and 0.5% for the background, unknown, low, and high current dioxin categories,  $p = 0.262$ ). No adjusted analysis was done because there were few abnormalities.

**TABLE 10-26.**  
**Analysis of LDH (U/L)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> <0.001)	Low	130	130.0	-0.0031 (0.0058)	0.599
	Medium	257	128.3		
	High	130	128.7		
b) Maximal (n=737) (R <sup>2</sup> <0.001)	Low	184	127.6	0.0003 (0.0042)	0.935
	Medium	368	129.1		
	High	185	128.4		

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=514) (R <sup>2</sup> =0.031)	Low	130	130.0	-0.0024 (0.0059)	0.687	RACE*ALC (p=0.007) RACE*IC (p=0.029)
	Medium	255	129.0			
	High	129	129.2			
d) Maximal (n=737) (R <sup>2</sup> =0.023)	Low	184	125.6	0.0008 (0.0044)	0.864	IC (p=0.118) AGE*RACE (p=0.016) RACE*DC (p=0.030)
	Medium	368	126.6			
	High	185	126.3			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm LDH versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-26. (Continued)

Analysis of LDH (U/L)  
(Continuous)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.008)	≤18.6	130.9 (72)	126.2 (126)	126.5 (53)	-0.0141 (0.0095)	0.252 <sup>c</sup> 0.139 <sup>d</sup>	
	>18.6	130.7 (58)	130.0 (131)	129.6 (77)	-0.0000 (0.0078)	0.999 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.006)	≤18.6	126.2 (105)	128.2 (189)	126.0 (82)	-0.0047 (0.0066)	0.611 <sup>c</sup> 0.473 <sup>d</sup>	
	>18.6	130.0 (79)	129.8 (178)	130.6 (104)	-0.0003 (0.0058)	0.963 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=514) (R <sup>2</sup> =0.040)	≤18.6	130.6 (72)	126.2 (126)	126.0 (52)	-0.0141 (0.0095)	0.255 <sup>c</sup> 0.140 <sup>d</sup>	RACE*ALC (p=0.007) RACE*IC (p=0.027)
	>18.6	130.7 (58)	130.4 (129)	129.9 (77)	-0.0002 (0.0078)	0.982 <sup>d</sup>	
h) Maximal (n=737) (R <sup>2</sup> =0.028)	≤18.6	124.2 (105)	125.6 (189)	124.3 (82)	-0.0045 (0.0068)	0.677 <sup>c</sup> 0.510 <sup>d</sup>	IC (p=0.094) AGE*RACE (p=0.017) RACE*DC (p=0.033)
	>18.6	127.9 (79)	127.5 (178)	128.0 (104)	-0.0008 (0.0060)	0.889 <sup>d</sup>	

<sup>a</sup>Transformed from natural logarithm scale.<sup>b</sup>Slope and standard error based on natural logarithm LDH versus log<sub>2</sub> dioxin.<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-26. (Continued)**

**Analysis of LDH (U/L)  
(Continuous)**

<b>i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted</b>						
Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	
Background	779	127.9	All Categories		0.751	
Unknown	341	126.7	Unknown vs. Background	-1.2 --	0.361	
Low	193	127.6	Low vs. Background	-0.3 --	0.821	
High	186	128.6	High vs. Background	0.7 --	0.715	
Total	1,499		(R <sup>2</sup> <0.001)			
<b>j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted</b>						
Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	779	130.3	All Categories		0.725	AGE (p=0.007) RACE (p=0.019) DC (p=0.080)
Unknown	341	129.2	Unknown vs. Background	-1.1 --	0.450	
Low	193	129.8	Low vs. Background	-0.5 --	0.794	
High	186	131.4	High vs. Background	1.1 --	0.518	
Total	1,499		(R <sup>2</sup> =0.010)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>p-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

**TABLE 10-27.****Analysis of LDH  
(Discrete)**


---

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Abnormal High</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=517)	Low	130	0.8	0.60 (0.13,2.77)	0.470
	Medium	257	0.4		
	High	130	0.0		
b) Maximal (n=737)	Low	184	1.6	0.47 (0.18,1.28)	0.083
	Medium	368	0.3		
	High	185	0.5		

---

<sup>a</sup>Relative risk for a twofold increase in dioxin.Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-27. (Continued)

**Analysis of LDH  
(Discrete)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) <u>Current Dioxin</u>			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
c) Minimal (n=517)	≤18.6	1.4	0.0	0.0	--	--
		(72)	(126)	(53)		
	>18.6	0.0	0.8	0.0	--	--
		(58)	(131)	(77)		
d) Maximal (n=737)	≤18.6	2.9	0.5	0.0	0.27 (0.05,1.38)	0.116 <sup>b</sup>
		(105)	(189)	(82)		
	>18.6	0.0	0.0	1.0	--	--
		(79)	(178)	(104)		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

--: Relative risk/confidence interval/p-value not given due to the sparse number of abnormalities.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.



**TABLE 10-27. (Continued)**

**Analysis of LDH  
(Discrete)**

<b>e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted</b>					
<b>Current Dioxin Category</b>	<b>n</b>	<b>Percent Abnormal High</b>	<b>Contrast</b>	<b>Est. Relative Risk (95% C.I.)</b>	<b>p-Value</b>
Background	779	1.5	All Categories		0.262
Unknown	341	1.5	Unknown vs. Background	0.95 (0.33,2.72)	0.999
Low	193	0.0	Low vs. Background	—	0.138
High	186	0.5	High vs. Background	0.35 (0.05,2.67)	0.504
Total	1,499				

--: Relative risk and confidence interval not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.

Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.

Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .

High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

## Cholesterol (Continuous)

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, the unadjusted initial dioxin analyses did not find a significant association with cholesterol in its continuous form (Table 10-28 [a] and [b]:  $p=0.175$  and  $p=0.179$ , respectively). However, a significant positive slope was noted under both assumptions after covariate adjustment (Table 10-28 [c] and [d]:  $p=0.046$  and  $p=0.041$  for the minimal and maximal assumptions). The minimal analysis was adjusted for age, current alcohol use, and the degreasing chemical-by-industrial chemical use interaction. Current alcohol use and the age-by-race interaction were used for adjustment in the maximal analysis. Under the minimal assumption, the adjusted mean levels of cholesterol were 213.0, 214.4, and 218.8 mg/dl for the low, medium, and high initial dioxin categories. The corresponding means for the maximal cohort were 210.8, 211.1, and 216.0 mg/dl.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under the minimal assumption, the unadjusted current dioxin and time since tour analysis for cholesterol detected a marginally significant interaction between current dioxin and time (Table 10-28 [e]:  $p=0.069$ ). The association between current dioxin and cholesterol was significantly positive for Ranch Hands with an early tour in contrast to a nonsignificant negative association for Ranch Hands with a later tour (time $>18.6$ : Adj. slope $=0.0195$ ,  $p=0.024$ ; time $\leq 18.6$ : Adj. slope $=-0.0053$ ,  $p=0.612$ ). For Ranch Hands with an early tour, the mean levels of cholesterol were 210.3, 216.2, and 221.4 mg/dl for the low, medium, and high current dioxin categories. The unadjusted analysis for the maximal cohort did not find a significant current dioxin-by-time interaction (Table 10-28 [f]:  $p=0.335$ ).

After covariate adjustment, the current dioxin-by-time interaction became significant for the minimal cohort (Table 10-28 [g]:  $p=0.049$ ), with the association between current dioxin and cholesterol remaining significant for Ranch Hands with an early tour (time $>18.6$ : Adj. slope $=0.0277$ ,  $p=0.002$ ; Adj. means: 205.6, 213.7, and 221.5 mg/dl for the low, medium, and high current dioxin categories). The association between current dioxin and cholesterol was not significant for Ranch Hands with a later tour (time $\leq 18.6$ : Adj. slope $=0.0011$ ,  $p=0.921$ ).

The adjusted maximal analysis detected a significant current dioxin-by-time-by-lifetime alcohol history interaction (Table 10-28 [h]:  $p=0.034$ ). The lifetime alcohol history covariate was trichotomized (0 drink-years,  $>0-40$  drink-years,  $>40$  drink-years) to explore the interaction. Appendix Table I-1 shows that the current dioxin-by-time interaction was not significant for each lifetime alcohol history stratum (0 drink-years:  $p=0.952$ ;  $>0-40$  drink-years:  $p=0.916$ ;  $>40$  drink-years:  $p=0.152$ ). The association between current dioxin and cholesterol was not significant within each time stratum, except for a marginally significant positive finding for heavy lifetime drinkers who had an early tour ( $>40$  drink-years, time $>18.6$ :  $p=0.059$ ). The current dioxin-by-time interaction was not significant (Table 10-28 [h]:  $p=0.415$ ) after excluding the current dioxin-by-time-by-lifetime alcohol history interaction. The association between current dioxin and cholesterol was significant for Ranch Hands with an early tour (time $>18.6$ :  $p=0.030$ ).

**TABLE 10-28.**  
**Analysis of Cholesterol (mg/dl)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Mean<sup>a</sup></b>	<b>Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>
a) Minimal (n=517) (R <sup>2</sup> =0.004)	Low	130	215.7	0.0088 (0.0065)	0.175
	Medium	257	215.9		
	High	130	218.1		
b) Maximal (n=737) (R <sup>2</sup> =0.002)	Low	184	215.2	0.0066 (0.0049)	0.179
	Medium	368	215.5		
	High	185	217.9		

  

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>						
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Adj. Mean<sup>a</sup></b>	<b>Adj. Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c) Minimal (n=514) (R <sup>2</sup> =0.041)	Low	130	213.0	0.0133 (0.0066)	0.046	AGE (p=0.007) ALC (p=0.016) DC*IC (p=0.049)
	Medium	255	214.4			
	High	129	218.8			
d) Maximal (n=732) (R <sup>2</sup> =0.030)	Low	183	210.8	0.0102 (0.0050)	0.041	ALC (p=0.006) AGE*RACE (p=0.035)
	Medium	365	211.1			
	High	184	216.0			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm cholesterol versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-28. (Continued)**  
**Analysis of Cholesterol (mg/dl)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.010)	≤18.6	216.6 (72)	218.4 (126)	211.4 (53)	-0.0053 (0.0105)	0.069 <sup>c</sup> 0.612 <sup>d</sup>	
	>18.6	210.3 (58)	216.2 (131)	221.4 (77)	0.0195 (0.0086)	0.024 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.003)	≤18.6	213.1 (105)	216.7 (189)	215.8 (82)	0.0007 (0.0076)	0.335 <sup>c</sup> 0.931 <sup>d</sup>	
	>18.6	217.6 (79)	213.5 (178)	221.0 (104)	0.0104 (0.0067)	0.120 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=514) (R <sup>2</sup> =0.053)	≤18.6	214.3 (72)	218.4 (126)	213.2 (52)	0.0011 (0.0108)	0.049 <sup>c</sup> 0.921 <sup>d</sup>	AGE (p=0.004) ALC (p=0.013) DC*IC (p=0.028)
	>18.6	205.6 (58)	213.7 (129)	221.5 (77)	0.0277 (0.0088)	0.002 <sup>d</sup>	
h) Maximal (n=728) (R <sup>2</sup> =0.040)	≤18.6	208.7** (104)	213.2** (188)	215.5** (80)	0.0065 (0.0077)**	0.415*** 0.398*** <sup>d</sup>	CURR*TIME*DRKYR (p=0.034) ALC (p=0.018)
	>18.6	212.5** (78)	208.3** (176)	218.5** (102)	0.0147 (0.0068)**	0.030*** <sup>d</sup>	AGE*RACE (p=0.033)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm cholesterol versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-28. (Continued)**  
**Analysis of Cholesterol (mg/dl)**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	213.3	All Categories		0.386
Unknown	341	214.3	Unknown vs. Background	1.0 --	0.669
Low	193	215.0	Low vs. Background	1.7 --	0.570
High	186	218.7	High vs. Background	5.4 --	0.085
Total	1,499		(R <sup>2</sup> =0.002)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	777	212.9	All Categories		0.229	ALC (p=0.029) IC (p=0.099)
Unknown	338	214.1	Unknown vs. Background	1.2 --	0.612	AGE*DRKYR (p=0.022)
Low	191	214.5	Low vs. Background	1.6 --	0.608	
High	182	219.5	High vs. Background	6.6 --	0.038	
Total	1,488		(R <sup>2</sup> =0.020)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.  
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted analysis of categorized current dioxin found that the mean cholesterol for the high current dioxin category was marginally more than the background mean (Table 10-28 [i]: 218.7 mg/dl versus 213.3 mg/dl,  $p=0.085$ ), although the overall contrast was not significant ( $p=0.386$ ). After covariate adjustment, the high versus background contrast became significant (Table 10-28 [j]: 219.5 mg/dl versus 212.9 mg/dl,  $p=0.038$ ), and the overall category contrast remained nonsignificant ( $p=0.229$ ). The unknown versus background and the low versus background contrasts were not significant for either the unadjusted or adjusted analysis ( $p>0.50$  for each contrast).

### **Cholesterol (Discrete)**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

For both cohorts, the unadjusted and adjusted initial dioxin analyses did not detect a significant relative risk of abnormally high cholesterol levels (Table 10-29 [a-d]:  $p>0.35$  for all analyses).

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The unadjusted analyses of discretized cholesterol did not find a significant current dioxin-by-time since tour interaction under either the minimal (Table 10-29 [e]:  $p=0.388$ ) or maximal (Table 10-29 [f]:  $p=0.837$ ) assumption.

The current dioxin-by-time interaction remained nonsignificant for the maximal cohort (Table 10-29 [h]:  $p=0.872$ ) after adjustment for age and industrial chemical exposure. However, the adjusted minimal analysis detected a significant current dioxin-by-time-by-industrial chemical exposure interaction (Table 10-29 [g]:  $p=0.008$ ). Stratified results showed a marginally significant interaction between current dioxin and time for Ranch Hands who had never been exposed to industrial chemicals (Appendix Table I-1:  $p=0.060$ ), but the association between current dioxin and cholesterol was not significant within each time stratum (time $\leq$ 18.6: Adj. RR=1.73,  $p=0.102$ ; time $>$ 18.6: Adj. RR= 0.75,  $p=0.369$ ). The current dioxin-by-time interaction was significant for Ranch Hands who had been exposed to industrial chemicals ( $p=0.030$ ). The adjusted relative risk of an abnormally high level of cholesterol was marginally less than 1 for these Ranch Hands with a later tour (time $\leq$ 18.6: Adj. RR=0.67,  $p=0.083$ ), and it was greater than 1, but not significant, for those with an early tour (time $>$ 18.6: Adj. RR=1.22,  $p=0.261$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis, the percentages of abnormally high levels of cholesterol did not differ significantly among the four current dioxin categories (Table 10-29 [i]:  $p=0.164$ ), although the prevalence rate was significantly more in the unknown current dioxin category than in the background category (16.1% versus 11.2%, Est. RR=1.53, 95% C.I.: [1.06,2.20],  $p=0.022$ ). The prevalence rates in the low (13.0%) and high (12.4%) current dioxin categories were not significantly different from the background rate ( $p=0.487$  and  $p=0.644$ , respectively). The adjusted analysis displayed similar results. The overall contrast was not significant (Table 10-29 [j]:  $p=0.141$ ), but the unknown versus background contrast was significant (Adj. RR=1.56, 95% C.I.: [1.08,2.24],  $p=0.018$ ).

**TABLE 10-29.**  
**Analysis of Cholesterol**  
**(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	16.2	0.93 (0.75,1.15)	0.472
	Medium	257	14.0		
	High	130	10.8		
b) Maximal (n=737)	Low	184	15.2	0.94 (0.80,1.09)	0.392
	Medium	368	15.5		
	High	185	11.4		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=517)	0.95 (0.76,1.18)	0.625	AGE (p=0.053) IC (p=0.044)
d) Maximal (n=737)	0.94 (0.80,1.11)	0.482	AGE (p=0.033) IC (P=0.110)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-29. (Continued)

**Analysis of Cholesterol  
(Discrete)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	15.3 (72)	15.9 (126)	9.4 (53)	0.83 (0.58,1.19)	0.388 <sup>b</sup> 0.309 <sup>c</sup>
	>18.6	15.5 (58)	13.0 (131)	11.7 (77)	1.01 (0.77,1.34)	0.924 <sup>c</sup>
f) Maximal (n=737)	≤18.6	15.2 (105)	14.8 (189)	13.4 (82)	0.91 (0.71,1.15)	0.837 <sup>b</sup> 0.427 <sup>c</sup>
	>18.6	15.2 (79)	15.2 (178)	11.5 (104)	0.94 (0.76,1.16)	0.556 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=517)	≤18.6	****		****	CURR*TIME*IC (p=0.008) AGE (p=0.053)	
	>18.6	****		****		
h) Maximal (n=737)	≤18.6	0.93 (0.72,1.19)		0.872 <sup>b</sup> 0.560 <sup>c</sup>	AGE (p=0.037) IC (p=0.114)	
	>18.6	0.95 (0.76,1.19)		0.672 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

\*\*\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (p≤0.01); adjusted relative risk, confidence interval, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.



**TABLE 10-29. (Continued)**

**Analysis of Cholesterol  
(Discrete)**

<b>i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted</b>					
Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	11.2	All Categories		0.164
Unknown	341	16.1	Unknown vs. Background	1.53 (1.06,2.20)	0.022
Low	193	13.0	Low vs. Background	1.18 (0.74,1.90)	0.487
High	186	12.4	High vs. Background	1.12 (0.69,1.83)	0.644
Total	1,499				
<b>j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted</b>					
Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.141	ALC (p=0.053)
Unknown	339	Unknown vs. Background	1.56 (1.08,2.24)	0.018	
Low	191	Low vs. Background	1.16 (0.72,1.88)	0.545	
High	185	High vs. Background	1.13 (0.69,1.84)	0.629	
Total	1,494				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

## **HDL (Continuous)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analyses did not find a significant association with HDL under the minimal assumption (Table 10-30 [a]:  $p=0.169$ ), but the association was significantly negative under the maximal assumption (Table 10-30 [b]:  $p<0.001$ ). For the maximal cohort, the unadjusted mean levels of HDL decreased with initial dioxin (47.56, 44.39, and 43.31 mg/dl for the low, medium, and high initial dioxin categories).

The association between HDL and initial dioxin remained nonsignificant for the adjusted minimal analysis (Table 10-30 [c]:  $p=0.218$ ). The adjusted analysis for the maximal cohort detected a significant interaction between initial dioxin and degreasing chemical exposure (Table 10-30 [d]:  $p=0.006$ ). Stratified results showed a highly significant negative association between initial dioxin and HDL for Ranch Hands who had never been exposed to degreasing chemicals (Appendix Table I-1,  $p<0.001$ ). The adjusted mean levels of HDL for the low, medium, and high initial dioxin categories in this stratum were 51.55, 45.34, and 44.65 mg/dl. The association between initial dioxin and HDL was negative, but not significant, for Ranch Hands who had been exposed to degreasing chemicals ( $p=0.200$ , Adj. means: 45.69, 44.80, and 44.12 for the low, medium, and high initial dioxin categories). After deleting the interaction, the adjusted maximal analysis displayed a highly significant negative association between initial dioxin and HDL (Table 10-30 [d]:  $p<0.001$ ), supporting the unadjusted analysis.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the unadjusted current dioxin and time since tour analyses of HDL in its continuous form did not find a significant current dioxin-by-time interaction (Table 10-30 [e] and [f]:  $p=0.920$  and  $p=0.727$ , respectively). However, under the maximal assumption, the association between current dioxin and HDL was significantly negative within each time stratum (time $\leq$ 18.6:  $p=0.008$ ; time $>$ 18.6:  $p=0.014$ ). The unadjusted mean levels of HDL decreased with current dioxin in both time strata (time $\leq$ 18.6: 48.51, 44.60, and 43.65 mg/dl for the low, medium, and high current dioxin categories; time $>$ 18.6: 47.58, 43.91, and 42.63 mg/dl for the corresponding categories).

The adjusted minimal analysis detected a significant current dioxin-by-time-by-industrial chemical exposure interaction (Table 10-30 [g]:  $p=0.026$ ). However, stratified results did not show a significant interaction between current dioxin and time, either for Ranch Hands who had never been exposed to industrial chemicals (Appendix Table I-1:  $p=0.115$ ) or for Ranch Hands who had been exposed to industrial chemicals ( $p=0.110$ ). The association between current dioxin and HDL was marginally negative for Ranch Hands with an early tour who had been exposed to industrial chemicals (time $>$ 18.6:  $p=0.065$ ). After excluding the current dioxin-by-time-by-industrial chemical exposure interaction, the adjusted minimal analysis did not find a significant interaction between current dioxin and time (Table 10-30 [g]:  $p=0.914$ ).

The adjusted maximal analysis supported the unadjusted findings. The current dioxin-by-time interaction was not significant (Table 10-30 [h]:  $p=0.748$ ), but a significant negative

**TABLE 10-30.**  
**Analysis of HDL (mg/dl)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Mean<sup>a</sup></b>	<b>Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>
a) Minimal (n=517) (R <sup>2</sup> =0.004)	Low	130	45.42	-0.0126 (0.0091)	0.169
	Medium	257	42.83		
	High	130	44.23		
b) Maximal (n=737) (R <sup>2</sup> =0.021)	Low	184	47.56	-0.0266 (0.0067)	<0.001
	Medium	368	44.39		
	High	185	43.31		

  

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>						
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Adj. Mean<sup>a</sup></b>	<b>Adj. Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c) Minimal (n=514) (R <sup>2</sup> =0.086)	Low	130	46.16	-0.0115 (0.0093)	0.218	ALC (p<0.001) AGE*RACE (p=0.017) RACE*IC (p=0.044)
	Medium	255	44.04			
	High	129	45.72			
d) Maximal (n=728) (R <sup>2</sup> =0.105)	Low	182	48.52***	-0.0231 (0.0069)***	<0.001***	INIT*DC (p=0.006) AGE*RACE (p=0.012) AGE*DC (p=0.010) ALC*DRKYR (p=0.005)
	Medium	365	45.35***			
	High	181	44.86***			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm HDL versus log<sub>2</sub> dioxin.

\*\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (p≤0.01); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-30. (Continued)

Analysis of HDL (mg/dl)  
(Continuous)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.004)	≤18.6	45.15 (72)	43.63 (126)	45.12 (53)	-0.0086 (0.0149)	0.920 <sup>c</sup> 0.566 <sup>d</sup>	
	>18.6	45.24 (58)	42.37 (131)	43.47 (77)	-0.0105 (0.0122)	0.389 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.020)	≤18.6	48.51 (105)	44.60 (189)	43.65 (82)	-0.0276 (0.0104)	0.727 <sup>c</sup> 0.008 <sup>d</sup>	
	>18.6	47.58 (79)	43.91 (178)	42.63 (104)	-0.0227 (0.0092)	0.014 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=514) (R <sup>2</sup> =0.100)	≤18.6	46.13** (72)	45.02** (126)	46.94** (52)	-0.0069 (0.0151)**	0.914*** 0.648*** <sup>d</sup>	CURR*TIME*IC (p=0.026) ALC (p<0.001) AGE*RACE (p=0.012) RACE*IC (p=0.050)
	>18.6	45.93** (58)	43.66** (129)	45.09** (77)	-0.0090 (0.0123)**	0.466*** <sup>d</sup>	
h) Maximal (n=728) (R <sup>2</sup> =0.090)	≤18.6	49.29 (104)	45.74 (188)	45.06 (80)	-0.0235 (0.0106)	0.748 <sup>c</sup> 0.027 <sup>d</sup>	DC (p=0.049) AGE*RACE (p=0.021) ALC*DRKYR (p=0.012)
	>18.6	48.96 (78)	44.73 (176)	44.08 (102)	-0.0191 (0.0094)	0.042 <sup>d</sup>	

<sup>a</sup>Transformed from natural logarithm scale.<sup>b</sup>Slope and standard error based on natural logarithm HDL versus log<sub>2</sub> dioxin.<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-30. (Continued)**

**Analysis of HDL (mg/dl)  
(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	44.98	All Categories		<0.001
Unknown	341	47.81	Unknown vs. Background	2.83 --	<0.001
Low	193	43.60	Low vs. Background	-1.38 --	0.115
High	186	43.07	High vs. Background	-1.91 --	0.031
Total	1,499		(R <sup>2</sup> =0.019)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	777	45.92**	All Categories		<0.001**	DXCAT*DRKYR (p=0.017)
Unknown	338	48.93**	Unknown vs. Background	3.01 -- **	<0.001**	AGE*RACE (p=0.025)
Low	191	44.85**	Low vs. Background	-1.07 -- **	0.219**	RACE*IC (p=0.023)
High	182	44.59**	High vs. Background	-1.33 -- **	0.137**	RACE*DC (p=0.023)
Total	1,488		(R <sup>2</sup> =0.106)			ALC*DRKYR (p=0.012)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of means on natural logarithm scale.

\*\*Categorized current dioxin-by-covariate interaction (0.01<p≤0.05); adjusted mean and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

association between current dioxin and HDL was noted within each time stratum (time $\leq$ 18.6: p=0.027; time>18.6: p=0.042).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis found that the mean levels of HDL differed significantly among current dioxin categories (Table 10-30 [i]: 44.98, 47.81, 43.60, and 43.07 mg/dl for the background, unknown, low, and high current dioxin categories, p<0.001). The low current dioxin category mean was significantly more than the background mean (p<0.001), while the high current dioxin category mean was significantly less than the background mean (p=0.031).

The adjusted analysis detected a significant current dioxin-by-lifetime alcohol history interaction (Table 10-30 [j]: p=0.017). To explore the interaction, the lifetime alcohol history covariate was categorized into three levels: never (0 drink-years), moderate (>0-40 drink-years), and heavy (>40 drink-years). The adjusted mean levels of HDL did not differ significantly among current dioxin categories for participants who never had drunk alcohol (Appendix Table I-1: 43.77, 45.01, 46.00, and 46.62 mg/dl for the background, unknown, low, and high current dioxin categories, p=0.657) or for heavy lifetime drinkers (46.77, 46.65, 43.78, and 44.63 for the corresponding categories, p=0.315). Of the four current dioxin categories, the background mean was lowest for participants who never had drunk alcohol, but it was highest for heavy drinkers. The overall difference among adjusted mean levels was significant for moderate drinkers (46.01, 50.16, 45.24, and 44.06 mg/dl for the background, unknown, low, and high current dioxin categories, p<0.001). The mean HDL for the unknown category was significantly more than the background mean (p<0.001), but the mean for the high category was marginally less than the background mean (p=0.083). The low versus background contrast was not significant (p=0.455).

After excluding the interaction, the adjusted analysis found a highly significant overall difference in mean levels of HDL among the current dioxin categories (Table 10-30 [j]: 45.92, 48.93, 44.85, and 44.59 mg/dl for the background, unknown, low, and high current dioxin categories, p<0.001). As in the unadjusted analysis, the unknown versus background contrast was highly significant (p<0.001), but the high versus background contrast became nonsignificant after covariate adjustment (p=0.137).

**HDL (Discrete)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Both the unadjusted and adjusted initial dioxin analyses of discretized HDL did not detect a significant relative risk of an abnormally low level of HDL (Table 10-31 [a-d]: p>0.35 for the minimal and maximal analyses).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The current dioxin-by-time since tour interaction was not significant for the discrete analyses of HDL (Table 10-31 [e-h]: p>0.50 for each unadjusted and adjusted analysis).

TABLE 10-31.

Analysis of HDL  
(Discrete)

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal Low	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	0.8	1.18 (0.83,1.68)	0.357
	Medium	257	5.1		
	High	130	3.8		
b) Maximal (n=737)	Low	184	2.7	1.11 (0.85,1.46)	0.439
	Medium	368	3.3		
	High	185	4.9		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=514)	1.17 (0.82,1.67)	0.391	ALC (p=0.024)
d) Maximal (n=732)	1.11 (0.84,1.45)	0.476	RACE (p=0.111) ALC (p=0.053)

<sup>a</sup>Relative risk for a twofold increase in dioxin.Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-31. (Continued)

Analysis of HDL  
(Discrete)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal Low/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	0.0 (72)	4.8 (126)	1.9 (53)	1.24 (0.64,2.38)	0.705 <sup>b</sup> 0.519 <sup>c</sup>
	>18.6	1.7 (58)	6.1 (131)	3.9 (77)	1.06 (0.68,1.66)	0.787 <sup>c</sup>
f) Maximal (n=737)	≤18.6	3.8 (105)	2.6 (189)	3.7 (82)	0.99 (0.62,1.59)	0.587 <sup>b</sup> 0.982 <sup>c</sup>
	>18.6	1.3 (79)	3.4 (178)	6.7 (104)	1.17 (0.82,1.65)	0.382 <sup>c</sup>
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=514)	≤18.6	1.23 (0.64,2.35)		0.538 <sup>c</sup>	RACE (p=0.141)	
	>18.6	1.02 (0.65,1.60)		0.936 <sup>c</sup>	ALC (p=0.023)	
h) Maximal (n=732)	≤18.6	0.98 (0.61,1.57)		0.937 <sup>c</sup>	RACE (p=0.106)	
	>18.6	1.16 (0.82,1.64)		0.413 <sup>c</sup>	ALC (p=0.052)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.



TABLE 10-31. (Continued)

**Analysis of HDL  
(Discrete)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal Low	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	3.6	All Categories		0.721
Unknown	341	3.5	Unknown vs. Background	0.98 (0.49,1.95)	0.950
Low	193	4.1	Low vs. Background	1.16 (0.52,2.59)	0.717
High	186	5.4	High vs. Background	1.52 (0.73,3.20)	0.265
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.834**	DXCAT*DC (p=0.025) ALC (p=0.002)
Unknown	339	Unknown vs. Background	1.01 (0.50,2.02)**	0.978**	
Low	191	Low vs. Background	1.12 (0.50,2.51)**	0.778**	
High	185	High vs. Background	1.42 (0.67,3.00)**	0.356**	
Total	1,494				

\*\*Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

For the unadjusted analysis, the prevalence of abnormally low levels of HDL did not differ significantly among the four current dioxin categories (Table 10-31 [i]: 3.6%, 3.5%, 4.1%, and 5.4% for the background, unknown, low, and high current dioxin categories,  $p=0.721$ ).

The adjusted analysis detected a significant categorized current dioxin-by-degreasing chemical exposure interaction (Table 10-31 [j]:  $p=0.025$ ). Stratified results found a marginally significant overall contrast for participants who had never been exposed to degreasing chemicals (Appendix Table I-1:  $p=0.058$ ). The percentages of abnormally low levels of HDL in this stratum were 2.0, 4.8, 0.0, and 7.1 percent for the background, unknown, low, and high current dioxin categories. The adjusted relative risk for the high versus background contrast was of borderline significance (Adj. RR=3.43, 95% C.I.: [0.82,14.37],  $p=0.091$ ). The overall contrast was not significant for participants who had been exposed to degreasing chemicals ( $p=0.429$ ). After excluding the interaction, the results of the adjusted analysis were not significant (Table 10-31 [j]:  $p>0.35$  for all contrasts).

**Cholesterol-HDL Ratio (Continuous)**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, the unadjusted initial dioxin analyses found a significant positive association with the cholesterol-HDL ratio (Table 10-32 [a] and [b]:  $p=0.031$  and  $p<0.001$ , respectively). For the low, medium, and high initial dioxin categories, the mean ratios were 4.75, 5.04, and 4.93 in the minimal cohort and 4.52, 4.85, and 5.03 in the maximal cohort.

Adjusting for age, race, current alcohol use, and industrial chemical exposure, the association between initial dioxin and the cholesterol-HDL ratio remained significant under the minimal assumption (Table 10-32 [c]:  $p=0.009$ ). The adjusted mean ratios for the low, medium, and high initial dioxin categories were 4.42, 4.70, and 4.61. The adjusted analysis under the maximal assumption detected a significant initial dioxin-by-degreasing chemical exposure interaction (Table 10-32 [d]:  $p=0.010$ ). Appendix Table I-1 presents stratified results that show a highly significant positive association between initial dioxin and the cholesterol-HDL ratio for Ranch Hands who never had been exposed to degreasing chemicals (Adj. slope=0.0633,  $p<0.001$ ; Adj. means: 3.98, 4.63, and 4.87 for the low, medium, and high initial dioxin categories). The positive association between initial dioxin and the cholesterol-HDL ratio also was significant for Ranch Hands who had been exposed to degreasing chemicals (Adj. slope=0.0221,  $p=0.015$ ; Adj. means: 4.64, 4.64, and 4.87 for the low, medium, and high initial dioxin categories).

After excluding the interaction, the adjusted analysis under the maximal assumption displayed a highly significant positive association between initial dioxin and the cholesterol-HDL ratio (Table 10-32 [d]: Adj. slope=0.0350,  $p<0.001$ ). The adjusted mean ratios were 4.30, 4.60, and 4.79 for the low, medium, and high initial dioxin categories.

TABLE 10-32.

**Analysis of Cholesterol-HDL Ratio  
(Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> =0.009)	Low	130	4.75	0.0214 (0.0099)	0.031
	Medium	257	5.04		
	High	130	4.93		
b) Maximal (n=737) (R <sup>2</sup> =0.027)	Low	184	4.52	0.0332 (0.0074)	<0.001
	Medium	368	4.85		
	High	185	5.03		

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=514) (R <sup>2</sup> =0.066)	Low	130	4.42	0.0263 (0.0101)	0.009	AGE (p=0.001)
	Medium	255	4.70			RACE (p=0.005)
	High	129	4.61			ALC (p=0.003) IC (p=0.111)
d) Maximal (n=732) (R <sup>2</sup> =0.063)	Low	183	4.30***	0.0350 (0.0076)***	<0.001***	INIT*DC (p=0.010)
	Medium	365	4.60***			AGE (p=0.006)
	High	184	4.79***			RACE (p=0.065) ALC (p=0.003)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm cholesterol-HDL ratio versus log<sub>2</sub> dioxin.

\*\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (p≤0.01); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-32. (Continued)**  
**Analysis of Cholesterol-HDL Ratio**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.012)	≤18.6	4.80 (72)	5.01 (126)	4.69 (53)	0.0032 (0.0162)	0.200 <sup>c</sup> 0.841 <sup>d</sup>	
	>18.6	4.65 (58)	5.10 (131)	5.09 (77)	0.0300 (0.0132)	0.023 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.025)	≤18.6	4.39 (105)	4.86 (189)	4.94 (82)	0.0282 (0.0115)	0.749 <sup>c</sup> 0.015 <sup>d</sup>	
	>18.6	4.57 (79)	4.86 (178)	5.18 (104)	0.0331 (0.0101)	0.001 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=514) (R <sup>2</sup> =0.093)	≤18.6	**** (72)	**** (126)	**** (52)	****	****	CURR*TIME*IC (p=0.010)
	>18.6	**** (58)	**** (129)	**** (77)	****	****	AGE (p=0.002) ALC (p=0.002) RACE*IC (p=0.019)
h) Maximal (n=732) (R <sup>2</sup> =0.054)	≤18.6	4.22 (105)	4.63 (188)	4.78 (81)	0.0315 (0.0118)	0.711 <sup>c</sup> 0.008 <sup>d</sup>	AGE (p=0.007) RACE (p=0.078) ALC (p=0.003)
	>18.6	4.32 (78)	4.63 (176)	4.98 (104)	0.0371 (0.0104)	<0.001 <sup>d</sup>	IC (p=0.056)

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm cholesterol-HDL ratio versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

\*\*\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (p≤0.01); adjusted mean, adjusted slope, standard error, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-32. (Continued)**  
**Analysis of Cholesterol-HDL Ratio**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	4.74	All Categories		<0.001
Unknown	341	4.48	Unknown vs. Background	-0.26 --	0.002
Low	193	4.93	Low vs. Background	0.19 --	0.082
High	186	5.08	High vs. Background	0.34 --	0.003
Total	1,499		(R <sup>2</sup> =0.019)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	777	4.63	All Categories		<0.001	AGE (p=0.021) RACE (p=0.134)
Unknown	338	4.36	Unknown vs. Background	-0.27 --	<0.001	IC (p=0.004)
Low	191	4.79	Low vs. Background	0.16 --	0.136	ALC*DRKYR
High	182	4.96	High vs. Background	0.33 --	0.003	(p=0.031)
Total	1,488		(R <sup>2</sup> =0.061)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted analyses, the current dioxin-by-time since tour interaction was not significant for the cholesterol-HDL ratio under both the minimal (Table 10-32 [e]:  $p=0.200$ ) and maximal (Table 10-32 [f]:  $p=0.749$ ) assumptions. However, under both assumptions, the association between current dioxin and the cholesterol-HDL ratio was significantly positive for Ranch Hands with an early tour (time>18.6:  $p=0.023$  and  $p=0.001$  under the minimal and maximal assumptions). The mean ratios for the low, medium, and high current dioxin categories were 4.65, 5.10, and 5.09 under the minimal assumption. Under the maximal assumption, the corresponding means were 4.57, 4.86, and 5.18. For Ranch Hands with a later tour, the unadjusted association between current dioxin and the cholesterol-HDL ratio was not significant under the minimal assumption ( $p=0.841$ ), but it was significant under the maximal assumption ( $p=0.015$ ).

The adjusted minimal analysis detected a significant current dioxin-by-time-by-industrial chemical exposure interaction (Table 10-32 [g]:  $p=0.010$ ). Stratified results showed that the current dioxin-by-time interaction was not significant for Ranch Hands who never had been exposed to industrial chemicals (Appendix Table I-1:  $p=0.217$ ), although the association between current dioxin and the cholesterol-HDL ratio was marginally positive for these Ranch Hands with a later tour (time≤18.6:  $p=0.080$ , Adj. means: 4.56, 4.64, and 5.25 for the low, medium, and high current dioxin categories). By contrast, the interaction between current dioxin and time was significant for Ranch Hands who had been exposed to industrial chemicals ( $p=0.008$ ), with a significantly positive association between current dioxin and the cholesterol-HDL ratio for those with an early tour (time>18.6:  $p<0.001$ , Adj. means: 3.86, 4.61, and 4.70 for the low, medium, and high current dioxin categories).

Results from the adjusted maximal analysis supported the unadjusted findings. The interaction between current dioxin and time was not significant (Table 10-32 [h]:  $p=0.711$ ), but the association between current dioxin and the cholesterol-HDL ratio was significantly positive within each time stratum (time≤18.6:  $p=0.008$ ; time>18.6:  $p<0.001$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis found that the mean cholesterol-HDL ratios differed significantly among the categories (Table 10-32 [i]: 4.74, 4.48, 4.93, and 5.08 for the background, unknown, low, and high current dioxin categories,  $p<0.001$ ). All three Ranch Hand versus background contrasts were significant or marginally significant. The mean cholesterol-HDL ratio for the unknown current dioxin category was significantly less than the background mean ( $p=0.002$ ), the low current dioxin category mean ratio was marginally more than the background mean ( $p=0.082$ ), and the high current dioxin category mean was significantly more than the background mean ( $p=0.003$ ).

The adjusted analysis displayed similar findings except that the low versus background contrast was not significant. The overall contrast remained highly significant (Table 10-32 [j]:  $p<0.001$ ). The adjusted mean cholesterol-HDL ratios were 4.63, 4.36, 4.79, and 4.96 for the background, unknown, low, and high current dioxin categories. The mean ratio for the unknown category was significantly less than the mean background ratio ( $p<0.001$ ), and the high current dioxin category mean ratio was significantly more than the mean background ratio ( $p=0.003$ ).

## **Cholesterol-HDL Ratio (Discrete)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

In the unadjusted initial dioxin analyses, the estimated relative risk of an abnormally high cholesterol-HDL ratio was marginally significant under the minimal assumption (Table 10-33 [a]: Est. RR=1.14,  $p=0.077$ ) and highly significant under the maximal assumption (Table 10-33 [b]: Est. RR=1.22,  $p<0.001$ ). The percentages of abnormally high ratios for the low, medium, and high initial dioxin categories were 44.6, 50.2, and 48.5 percent in the minimal cohort, and 37.0, 45.9, and 50.3 percent in the maximal cohort.

After adjusting for current alcohol use and the age-by-degreasing chemical exposure interaction, the relative risk became significant for the minimal cohort (Table 10-33 [c]: Adj. RR=1.25,  $p=0.004$ ). The adjusted maximal analysis detected two significant initial dioxin-by-covariate interactions: initial dioxin-by-age (Table 10-33 [d]:  $p=0.008$ ) and initial dioxin-by-degreasing chemical exposure ( $p=0.001$ ). Age was dichotomized to explore the interaction. Appendix Table I-1 presents stratified results for the four combinations of age and degreasing chemical exposure categories. The adjusted relative risk was significantly greater than 1 in three of the four strata (born $\geq$ 1942, never had been exposed to degreasing chemicals: Adj. RR=1.49,  $p=0.001$ ; born $\geq$ 1942, had been exposed to degreasing chemicals: Adj. RR=1.00,  $p=0.999$ ; born<1942, never had been exposed to degreasing chemicals: Adj. RR=1.89,  $p<0.001$ ; born<1942, had been exposed to degreasing chemicals: Adj. RR=1.27,  $p=0.012$ ). After deleting the interactions, the adjusted maximal analysis displayed a highly significant relative risk (Table 10-33 [d]: Adj. RR=1.25,  $p<0.001$ ), supporting the unadjusted finding.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant for the unadjusted analyses of the discretized cholesterol-HDL ratio (Table 10-33 [e] and [f]:  $p=0.113$  and  $p=0.399$ , respectively), although the estimated relative risk of an abnormally high ratio was significant for Ranch Hands with an early tour (time>18.6: Est. RR=1.23,  $p=0.039$  in the minimal analysis; Est. RR=1.24,  $p=0.005$  in the maximal analysis). In this time stratum, the percentages of abnormally high ratios were 39.7, 55.7, and 55.8 percent for the minimal low, medium, and high current dioxin categories and 40.5, 48.9, and 55.8 percent for the corresponding maximal categories.

The adjusted minimal analysis detected a significant current dioxin-by-time-by-industrial chemical exposure interaction (Table 10-33 [g]:  $p=0.033$ ). Stratified results showed a significant current dioxin-by-time interaction for Ranch Hands who had been exposed to industrial chemicals (Appendix Table I-1:  $p=0.008$ ). For these Ranch Hands, there was a significant relative risk of an abnormally high cholesterol-HDL ratio for those with an early tour (time>18.6: Adj. RR=1.55,  $p=0.002$ ; % abnormal: 22.7%, 51.4%, and 57.4% for the low, medium, and high current dioxin categories). The relative risk was less than 1 but not significant for those with a later tour (time $\leq$ 18.6: Adj. RR=0.90,  $p=0.532$ ). The current dioxin-by-time interaction was not significant for Ranch Hands who never had been exposed to industrial chemicals ( $p=0.527$ ), although there was a marginally significant increased risk for those with a later tour (time $\leq$ 18.6: Adj. RR=1.46,  $p=0.089$ ; % abnormal: 43.8%, 36.7%, and 69.2% for the low, medium, and high current dioxin categories).

**TABLE 10-33.**  
**Analysis of Cholesterol-HDL Ratio**  
**(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	44.6	1.14 (0.99,1.31)	0.077
	Medium	257	50.2		
	High	130	48.5		
b) Maximal (n=737)	Low	184	37.0	1.22 (1.09,1.35)	<0.001
	Medium	368	45.9		
	High	185	50.3		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=514)	1.25 (1.07,1.46)	0.004	AGE*DC (p=0.016) ALC (p=0.006)
d) Maximal (n=732)	1.25 (1.12,1.40)***	<0.001***	INIT*AGE (p=0.008) INIT*DC (p=0.001) ALC (p=0.023)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

\*\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (p≤0.01); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.



**TABLE 10-33. (Continued)**  
**Analysis of Cholesterol-HDL Ratio**  
**(Discrete)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	47.2 (72)	45.2 (126)	37.7 (53)	0.96 (0.76,1.22)	0.113 <sup>b</sup> 0.741 <sup>c</sup>
	>18.6	39.7 (58)	55.7 (131)	55.8 (77)	1.23 (1.01,1.50)	0.039 <sup>c</sup>
f) Maximal (n=737)	≤18.6	32.4 (105)	44.4 (189)	42.7 (82)	1.12 (0.95,1.33)	0.399 <sup>b</sup> 0.168 <sup>c</sup>
	>18.6	40.5 (79)	48.9 (178)	55.8 (104)	1.24 (1.07,1.44)	0.005 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=514)	≤18.6	1.07 (0.84,1.37)**		0.119** <sup>b</sup>	CURR*TIME*IC (p=0.033)	
	>18.6	1.38 (1.11,1.70)**		0.582** <sup>c</sup>	ALC (p=0.007)	
				0.003** <sup>c</sup>	AGE*DC (p=0.015)	
h) Maximal (n=732)	≤18.6	1.14 (0.96,1.36)		0.283 <sup>b</sup>	ALC (p=0.026)	
	>18.6	1.29 (1.11,1.51)		0.132 <sup>c</sup>	AGE*DC (p=0.038)	
				0.001 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

\*\*Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-33. (Continued)**  
**Analysis of Cholesterol-HDL Ratio**  
**(Discrete)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	43.4	All Categories		0.021
Unknown	341	38.1	Unknown vs. Background	0.80 (0.62,1.04)	0.100
Low	193	49.2	Low vs. Background	1.26 (0.92,1.73)	0.145
High	186	50.0	High vs. Background	1.30 (0.95,1.80)	0.104
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.023	AGE (p=0.132) ALC (p<0.001) DC (p=0.100)
Unknown	339	Unknown vs. Background	0.80 (0.61,1.04)	0.091	
Low	191	Low vs. Background	1.23 (0.89,1.70)	0.202	
High	185	High vs. Background	1.33 (0.96,1.85)	0.087	
Total	1,494				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

After excluding the interaction, the adjusted minimal results were comparable to the unadjusted findings. The adjusted maximal analysis also displayed similar results. The interaction between current dioxin and time was not significant for either cohort (Table 10-33 [g] and [h]:  $p=0.119$  for the minimal cohort and  $p=0.283$  for the maximal cohort), but the relative risk was significant for Ranch Hands with an early tour (time $>18.6$ : Adj. RR=1.38,  $p=0.003$  for the minimal cohort; Adj. RR=1.29,  $p=0.001$  for the maximal cohort).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The percentage of abnormally high cholesterol-HDL ratios differed significantly among the current dioxin categories in the unadjusted analysis (Table 10-33 [i]: 43.4%, 38.1%, 49.2%, and 50.0% for the background, unknown, low, and high current dioxin categories,  $p=0.021$ ). The estimated relative risk for the unknown versus background contrast was marginally less than 1 (Adj. RR=0.80, 95% C.I.: [0.62,1.04],  $p=0.100$ ). The estimated relative risks for the low versus background and the high versus background contrasts were more than 1, but not significant ( $p=0.145$  and  $p=0.104$ , respectively). After adjustment for age, current alcohol use, and degreasing chemical exposure, the overall contrast remained significant (Table 10-33 [j]:  $p=0.023$ ) and the low versus background relative risk remained marginally less than 1 (Adj. RR=0.80, 95% C.I.: [0.61,1.04],  $p=0.091$ ). The relative risk for the high versus background contrast became marginally more than 1 (Adj. RR=1.33, 95% C.I.: [0.96,1.85],  $p=0.087$ ).

### **Triglycerides (Continuous)**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted continuous analyses of triglycerides found a positive association with initial dioxin that was marginally significant for the minimal cohort (Table 10-34 [a]:  $p=0.068$ ) and highly significant for the maximal cohort (Table 10-34 [b]:  $p<0.001$ ). The mean levels of triglycerides for the low, medium, and high initial dioxin categories were 115.8, 144.2, and 125.9 mg/dl for the minimal cohort. The corresponding means increased with initial dioxin for the maximal cohort (104.3, 128.9, and 137.5 mg/dl).

The adjusted analyses revealed a significant positive association between initial dioxin and triglycerides for both cohorts (Table 10-34 [c] and [d]:  $p=0.040$  and  $p<0.001$  for the minimal and maximal cohorts). The adjusted mean levels of triglycerides exhibited patterns similar to the unadjusted findings. For the minimal cohort, the adjusted mean level of triglycerides was highest for the medium initial dioxin category (101.3, 126.1, and 111.2 mg/dl for the low, medium, and high initial dioxin categories). The means increased for the maximal categories (90.3, 111.2, 119.8 mg/dl for the low, medium, and high categories).

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The current dioxin-by-time since tour interaction was not significant for the unadjusted analysis of triglycerides under the minimal assumption (Table 10-34 [e]:  $p=0.476$ ), but it was of borderline significance for the maximal assumption (Table 10-34 [f]:  $p=0.086$ ). For the maximal cohort, the positive association between current dioxin and triglycerides was highly significant for Ranch Hands with a later tour (time $\leq 18.6$ :  $p<0.001$ ), and marginally significant for Ranch Hands with an early tour (time $>18.6$ :  $p=0.094$ ). The mean levels of triglycerides for the later time stratum were 98.0, 125.2, and 141.9 mg/dl for the low, medium,

**TABLE 10-34.**

**Analysis of Triglycerides (mg/dl)  
(Continuous)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean <sup>a</sup>	Slope (Std. Error) <sup>b</sup>	p-Value
a) Minimal (n=517) (R <sup>2</sup> =0.006)	Low	130	115.8	0.0416 (0.0227)	0.068
	Medium	257	144.2		
	High	130	125.9		
b) Maximal (n=737) (R <sup>2</sup> =0.025)	Low	184	104.3	0.0733 (0.0169)	<0.001
	Medium	368	128.9		
	High	185	137.5		

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean <sup>a</sup>	Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
c) Minimal (n=511) (R <sup>2</sup> =0.031)	Low	130	101.3	0.0487 (0.0236)	0.040	RACE (p=0.016) AGE*DRKYR (p=0.041)
	Medium	253	126.1			
	High	128	111.2			
d) Maximal (n=728) (R <sup>2</sup> =0.055)	Low	182	90.3	0.0762 (0.0176)	<0.001	RACE (p=0.024) AGE*DRKYR (p=0.014) DRKYR*DC (p=0.035)
	Medium	365	111.2			
	High	181	119.8			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm triglycerides versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-34. (Continued)**  
**Analysis of Triglycerides (mg/dl)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.006)	≤18.6	111.0 (72)	143.5 (126)	128.7 (53)	0.0551 (0.0372)	0.476 <sup>c</sup> 0.139 <sup>d</sup>	
	>18.6	123.5 (58)	142.2 (131)	126.8 (77)	0.0208 (0.0303)	0.493 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> =0.025)	≤18.6	98.0 (105)	125.2 (189)	141.9 (82)	0.0993 (0.0264)	0.086 <sup>c</sup> <0.001 <sup>d</sup>	
	>18.6	114.7 (79)	133.9 (178)	131.2 (104)	0.0389 (0.0232)	0.094 <sup>d</sup>	
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=517) (R <sup>2</sup> =0.018)	≤18.6	98.1 (72)	124.7 (126)	110.5 (53)	0.0472 (0.0371)	0.525 <sup>c</sup> 0.205 <sup>d</sup>	RACE (p=0.011)
	>18.6	108.3 (58)	125.2 (131)	110.1 (77)	0.0168 (0.0302)	0.580 <sup>d</sup>	
h) Maximal (n=728) (R <sup>2</sup> =0.054)	≤18.6	86.2 (104)	109.5 (188)	124.9 (80)	0.1011 (0.0273)	0.135 <sup>c</sup> <0.001 <sup>d</sup>	RACE (p=0.027) AGE*DRKYR (p=0.018) DRKYR*DC (p=0.049)
	>18.6	98.7 (78)	114.8 (176)	115.1 (102)	0.0483 (0.0240)	0.045 <sup>d</sup>	

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm triglycerides versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-34. (Continued)**  
**Analysis of Triglycerides (mg/dl)**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	116.8	All Categories		<0.001
Unknown	341	104.1	Unknown vs. Background	-12.7 --	0.005
Low	193	140.0	Low vs. Background	23.2 --	<0.001
High	186	135.8	High vs. Background	19.0 --	0.004
Total	1,499		(R <sup>2</sup> =0.024)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	777	104.8**	All Categories		<0.001**	DXCAT*ALC (p=0.038) RACE (p=0.002)
Unknown	338	93.1**	Unknown vs. Background	-11.7 -- **	0.004**	AGE*DRKYR (p=0.014)
Low	191	124.1**	Low vs. Background	19.3 -- **	<0.001**	DRKYR*DC (p=0.041)
High	182	123.0**	High vs. Background	18.2 -- **	0.002**	
Total	1,488		(R <sup>2</sup> =0.051)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of means on natural logarithm scale.

\*\*Categorized current dioxin-by-covariate interaction (0.01<p≤0.05); adjusted mean and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.  
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.  
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.  
High (Ranch Hands): Current Dioxin >33.3 ppt.

and high current dioxin categories. The corresponding means for the early time stratum were 114.7, 133.9, and 131.2 mg/dl.

The interaction between current dioxin and time remained nonsignificant for the minimal cohort (Table 10-34 [g]:  $p=0.525$ ) and became nonsignificant for the maximal cohort (Table 10-34 [h]:  $p=0.135$ ) after adjustment for race, the age-by-lifetime alcohol history interaction, and the lifetime alcohol history-by-degreasing chemical exposure interaction. However, under the maximal assumption, the positive association between current dioxin and triglycerides was significant for both time strata (time $\leq$ 18.6:  $p<0.001$ ; time $>$ 18.6:  $p=0.045$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted mean levels of triglycerides differed significantly among the four current dioxin categories (Table 10-34 [i]: 116.8, 104.1, 140.0, and 135.8 mg/dl for the background, unknown, low, and high current dioxin categories,  $p<0.001$ ). Each contrast relative to the background category also was significant (unknown versus background:  $p=0.005$ ; low versus background:  $p<0.001$ ; high versus background:  $p=0.004$ ).

The adjusted analysis detected a significant interaction between categorized current dioxin and current alcohol use (Table 10-34 [j]:  $p=0.038$ ). To explore the interaction, the current alcohol use covariate was categorized into three levels: light ( $\leq$ 1 drink/day), moderate ( $>1$ -4 drinks/day), and heavy ( $>4$  drinks/day). The adjusted mean levels of triglycerides differed significantly among current dioxin categories for light drinkers (Appendix Table I-1: 106.2, 92.4, 122.2, and 126.7 mg/dl for the background, unknown, low, and high current dioxin categories,  $p<0.001$ ). In this stratum, the adjusted mean for the unknown current dioxin category was significantly less than the adjusted background mean ( $p=0.002$ ), but the adjusted means for the low and high categories were significantly more than the adjusted background mean ( $p=0.014$  and  $p=0.002$ , respectively).

The overall contrast was marginally significant for moderate drinkers ( $p=0.076$ ). The low current dioxin category had the largest adjusted mean triglycerides, which was significantly more than the background mean (133.8 mg/dl versus 103.2 mg/dl,  $p=0.030$ ). The adjusted means for the unknown current dioxin category (95.6 mg/dl) and the high current dioxin category (96.6 mg/dl) were not significantly different from the background mean ( $p=0.435$  and  $p=0.641$ , respectively). The overall current dioxin category contrast was not significant for heavy drinkers ( $p=0.129$ ), but the adjusted means increased by current dioxin category (72.7, 85.3, 103.0, and 134.4 mg/dl for the background, unknown, low, and high current dioxin categories). The high versus background contrast was significant ( $p=0.021$ ).

Excluding the interaction, the adjusted results paralleled the unadjusted findings. The overall difference in adjusted mean levels of triglycerides among current dioxin categories was highly significant (Table 10-34 [j]: 104.8, 93.1, 124.1, and 123.0 mg/dl for the background, unknown, low, and high current dioxin categories,  $p<0.001$ ) as were the three Ranch Hand versus background category contrasts ( $p<0.01$  for each contrast).

## **Triglycerides (Discrete)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, the unadjusted initial dioxin analyses showed a significant relative risk of abnormally high levels of triglycerides (Table 10-35 [a]: Est. RR=1.32,  $p=0.021$  for the minimal cohort; Table 10-35 [b]: Est. RR=1.31,  $p=0.004$  for the maximal cohort). The percentages of abnormal triglycerides levels were 3.8, 10.1, and 10.8 percent for the low, medium, and high initial dioxin categories of the minimal cohort. The corresponding percentages for the maximal cohort were 4.9, 6.8, and 11.9 percent.

The adjusted analyses results also were significant, with relative risk estimates essentially unchanged from the unadjusted analyses (Table 10-35 [c] and [d]: Adj. RR=1.32,  $p=0.026$  for the minimal cohort; Adj. RR=1.30,  $p=0.005$  for the maximal cohort).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The interaction between current dioxin and time since tour was not significant for the unadjusted analyses of discretized triglycerides (Table 10-35 [e] and [f]:  $p=0.948$  and  $p=0.814$ , for the minimal and maximal assumptions). However, the relative risk of an abnormally high level of triglycerides was significant in both time strata under the maximal assumption (time $\leq$ 18.6: Est. RR=1.35,  $p=0.045$ ; time $>$ 18.6: Est. RR=1.29,  $p=0.044$ ). Under the minimal assumption, the relative risk was marginally significant for Ranch Hands with an early tour (time $>$ 18.6: Est. RR=1.30,  $p=0.094$ ).

The current dioxin-by-time interaction remained nonsignificant in the adjusted analyses (Table 10-35 [g] and [h]:  $p=0.862$  and  $p=0.812$  for the minimal and maximal cohorts). Under the maximal assumption, the adjusted relative risks within each time stratum were essentially unchanged from the unadjusted findings (time $\leq$ 18.6: Adj. RR=1.34,  $p=0.050$ ; time $>$ 18.6: Adj. RR=1.28,  $p=0.052$ ). The adjusted relative risk remained marginally significant under the minimal assumption for Ranch Hands with an early tour (time $>$ 18.6: Adj. RR=1.32,  $p=0.078$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis found that the prevalence of abnormally high levels of triglycerides differed significantly among the four current dioxin categories (Table 10-35 [i]: 5.4%, 3.2%, 9.3%, and 11.8% for the background, unknown, low, and high current dioxin categories,  $p<0.001$ ). There was a significant increased risk relative to the background group for the low (Est. RR=1.80, 95% C.I.: [1.01,3.21],  $p=0.045$ ) and high (Est. RR=2.35, 95% C.I.: [1.37,4.05],  $p=0.002$ ) categories.

The adjusted analysis detected a significant interaction between categorized current dioxin and current alcohol use (Table 10-35 [j]:  $p=0.039$ ). This interaction also was noted in the categorized current dioxin analysis of triglycerides in its continuous form. Stratified results showed that the prevalence of abnormally high levels of triglycerides differed significantly among current dioxin categories for participants who currently consume no more than one drink per day (Appendix Table I-1: 5.2%, 2.2%, 8.4%, and 13.7% for the background, unknown, low, and high current dioxin categories,  $p<0.001$ ). The prevalence for the unknown category was significantly less than the background prevalence ( $p=0.035$ ), but the prevalence



**TABLE 10-35.**  
**Analysis of Triglycerides**  
**(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	3.8	1.32 (1.05,1.67)	0.021
	Medium	257	10.1		
	High	130	10.8		
b) Maximal (n=737)	Low	184	4.9	1.31 (1.10,1.57)	0.004
	Medium	368	6.8		
	High	185	11.9		

  

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=517)	1.32 (1.04,1.67)	0.026	RACE (p=0.031) DC*IC (p=0.025)
d) Maximal (n=732)	1.30 (1.09,1.56)	0.005	RACE (p=0.020) ALC (p=0.060)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-35. (Continued)

Analysis of Triglycerides  
(Discrete)

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	4.2 (72)	9.5 (126)	11.3 (53)	1.32 (0.89,1.95)	0.948 <sup>b</sup> 0.162 <sup>c</sup>
	>18.6	3.4 (58)	9.9 (131)	11.7 (77)	1.30 (0.96,1.76)	0.094 <sup>c</sup>
f) Maximal (n=737)	≤18.6	3.8 (105)	6.9 (189)	12.2 (82)	1.35 (1.01,1.80)	0.814 <sup>b</sup> 0.045 <sup>c</sup>
	>18.6	5.1 (79)	7.3 (178)	11.5 (104)	1.29 (1.01,1.64)	0.044 <sup>c</sup>
Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=517)				0.862 <sup>b</sup>	RACE (p=0.030)	
	≤18.6	1.27 (0.86,1.87)		0.238 <sup>c</sup>	DC*IC (p=0.024)	
	>18.6	1.32 (0.97,1.81)		0.078 <sup>c</sup>		
h) Maximal (n=732)				0.812 <sup>b</sup>	RACE (p=0.020)	
	≤18.6	1.34 (1.00,1.79)		0.050 <sup>c</sup>	ALC (p=0.060)	
	>18.6	1.28 (1.00,1.63)		0.052 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-35. (Continued)**

**Analysis of Triglycerides  
(Discrete)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	5.4	All Categories		<0.001
Unknown	341	3.2	Unknown vs. Background	0.58 (0.30,1.15)	0.120
Low	193	9.3	Low vs. Background	1.80 (1.01,3.21)	0.045
High	186	11.8	High vs. Background	2.35 (1.37,4.05)	0.002
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		<0.001**	DXCAT*ALC (p=0.039) AGE (p=0.143)
Unknown	339	Unknown vs. Background	0.56 (0.29,1.11)**	0.097**	RACE (p=0.025)
Low	191	Low vs. Background	1.81 (1.01,3.22)**	0.045**	
High	185	High vs. Background	2.55 (1.46,4.45)**	0.001**	
Total	1,494				

\*\*Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

for the high current dioxin category was significantly more than the background prevalence ( $p < 0.001$ ). There was no significant difference among current dioxin categories for moderate current drinkers (>1-4: 7.1%, 6.8%, 11.8%, and 0.0% for the background, unknown, low, and high current dioxin categories,  $p = 0.225$ ), but the overall contrast was marginally significant for heavy current heavy drinkers (>4:  $p = 0.051$ ). For the heavy current drinkers, the prevalences of abnormal triglycerides levels were 0.0 percent in the background category ( $n = 28$ ), 14.3 percent in the unknown category ( $n = 7$ ), 0.0 percent in the low category ( $n = 3$ ), and 12.5 percent in the high category ( $n = 8$ ).

After excluding the interaction, the adjusted analysis displayed results comparable to the unadjusted findings. The overall contrast was highly significant (Table 10-35 [j]:  $p < 0.001$ ) and the relative risk of an abnormal level of triglycerides was significantly more than 1 for the low versus background contrast (Adj. RR=1.81, 95% C.I.: [1.01,3.22],  $p = 0.045$ ) and also for the high versus background contrast (Adj. RR=2.55, 95% C.I.: [1.46,4.45],  $p = 0.001$ ). The relative risk for the unknown versus background contrast became marginally less than 1 after covariate adjustment (Adj. RR=0.56, 95% C.I.: [0.29,1.11],  $p = 0.097$ ).

#### **Creatine Kinase (Continuous)**

##### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analyses did not detect a significant association with creatine kinase in its continuous form under either the minimal (Table 10-36 [a]:  $p = 0.830$ ) or maximal (Table 10-36 [b]:  $p = 0.955$ ) assumptions. The adjusted analyses revealed a significant initial dioxin-by-age interaction under both assumptions (Table 10-36 [c] and [d]:  $p = 0.049$  and  $p = 0.040$  for the minimal and maximal assumptions). Age was dichotomized to explore the interaction. Under both assumptions, there was a significant negative association between initial dioxin and creatine kinase for Ranch Hands born before 1942 (Appendix Table I-1:  $p = 0.024$  and  $p = 0.039$  for the minimal and maximal assumptions). This contrasted with a positive association between initial dioxin and creatine kinase for Ranch Hands born in or after 1942. This association was marginally significant under the minimal assumption ( $p = 0.051$ ), but it was not significant under the maximal assumption ( $p = 0.158$ ). The adjusted analyses were not significant under both assumptions after excluding the initial dioxin-by-age interaction (Table 10-36 [c] and [d]:  $p = 0.824$  and  $p = 0.706$  for the minimal and maximal analyses).

##### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under both the minimal and maximal assumptions, the current dioxin and time since tour analyses for creatine kinase did not detect a significant interaction between current dioxin and time (Table 10-36 [e-h]:  $p > 0.45$  for the unadjusted and adjusted analyses).

##### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis of creatine kinase did not find a significant overall difference in the mean levels of creatine kinase (Table 10-36 [i]:  $p = 0.504$ ). However, the adjusted analysis detected a significant interaction between categorized current dioxin and race (Table 10-36 [j]:  $p = 0.027$ ). Stratified analyses found that the adjusted mean levels of creatine kinase differed significantly among current dioxin categories for Blacks (Appendix Table I-1: 247.4, 173.1, 176.3, and 182.4 mg/dl for the background,

**TABLE 10-36.**  
**Analysis of Creatine Kinase (U/L)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Mean<sup>a</sup></b>	<b>Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>
a) Minimal (n=517) (R <sup>2</sup> <0.001)	Low	130	113.4	-0.0036 (0.0170)	0.830
	Medium	257	109.1		
	High	130	112.8		
b) Maximal (n=737) (R <sup>2</sup> <0.001)	Low	184	111.6	-0.0007 (0.0124)	0.955
	Medium	368	109.5		
	High	185	113.1		

  

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>						
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Adj. Mean<sup>a</sup></b>	<b>Adj. Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c) Minimal (n=514) (R <sup>2</sup> =0.111)	Low	130	139.5**	-0.0038 (0.0169)**	0.824**	INIT*AGE (p=0.049) RACE*ALC (p=0.002) ALC*IC (p=0.049)
	Medium	255	135.6**			
	High	129	139.5**			
d) Maximal (n=737) (R <sup>2</sup> =0.090)	Low	184	148.8**	-0.0046 (0.0121)**	0.706**	INIT*AGE (p=0.040) RACE (p<0.001)
	Medium	368	142.5**			
	High	185	147.2**			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm creatine kinase versus log<sub>2</sub> dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.  
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-36. (Continued)**  
**Analysis of Creatine Kinase (U/L)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>							
Assumption	Time (Yrs.)	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R <sup>2</sup> =0.003)	≤18.6	119.9 (72)	108.5 (126)	116.7 (53)	-0.0134 (0.0277)	0.507 <sup>c</sup> 0.629 <sup>d</sup>	
	>18.6	104.3 (58)	109.3 (131)	111.7 (77)	0.0103 (0.0226)	0.647 <sup>d</sup>	
f) Maximal (n=737) (R <sup>2</sup> <0.001)	≤18.6	108.5 (105)	111.3 (189)	115.7 (82)	0.0079 (0.0193)	0.655 <sup>c</sup> 0.682 <sup>d</sup>	
	>18.6	114.1 (79)	107.8 (178)	111.9 (104)	-0.0036 (0.0170)	0.834 <sup>d</sup>	
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>							
Assumption	Time (Yrs.)	Adj. Mean <sup>a</sup> /(n) Current Dioxin			Adj. Slope (Std. Error) <sup>b</sup>	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=514) (R <sup>2</sup> =0.099)	≤18.6	147.4 (72)	136.5 (126)	145.5 (52)	-0.0115 (0.0275)	0.472 <sup>c</sup> 0.676 <sup>d</sup>	AGE (p=0.072) RACE*ALC (p=0.013)
	>18.6	130.9 (58)	135.2 (129)	141.1 (77)	0.0131 (0.0223)	0.556 <sup>d</sup>	
h) Maximal (n=737) (R <sup>2</sup> =0.085)	≤18.6	143.1 (105)	145.4 (189)	150.8 (82)	0.0057 (0.0189)	0.482 <sup>c</sup> 0.761 <sup>d</sup>	AGE (p=0.043) RACE (p<0.001)
	>18.6	155.0 (79)	140.8 (178)	144.6 (104)	-0.0116 (0.0167)	0.486 <sup>d</sup>	

\*Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on natural logarithm creatine kinase versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope different from 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-36. (Continued)**  
**Analysis of Creatine Kinase (U/L)**  
**(Continuous)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Mean <sup>a</sup>	Contrast	Difference of Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>
Background	779	109.4	All Categories		0.504
Unknown	341	106.2	Unknown vs. Background	-3.2 --	0.368
Low	193	107.1	Low vs. Background	-2.3 --	0.604
High	186	113.5	High vs. Background	4.1 --	0.374
Total	1,499		(R <sup>2</sup> =0.002)		

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Adj. Mean <sup>a</sup>	Contrast	Difference of Adj. Means (95% C.I.) <sup>e</sup>	p-Value <sup>f</sup>	Covariate Remarks
Background	779	151.6**	All Categories		0.683**	DXCAT*RACE (p=0.027)
Unknown	341	149.5**	Unknown vs. Background	-2.1 -- **	0.659**	AGE*DC (p=0.028)
Low	193	149.2**	Low vs. Background	-2.4 -- **	0.680**	
High	186	157.3**	High vs. Background	5.7 -- **	0.363**	
Total	1,499		(R <sup>2</sup> =0.114)			

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of means on natural logarithm scale.

\*\*Categorized current dioxin-by-covariate interaction (0.01 < p ≤ 0.05); adjusted mean and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤ 10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤ 10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤ 33.3 ppt.

High (Ranch Hands): Current Dioxin > 33.3 ppt.

unknown, low, and high current dioxin categories,  $p=0.031$ ). The adjusted means for the unknown and low categories were both significantly less than the background mean ( $p=0.023$  and  $p=0.045$ , respectively). The adjusted means did not differ significantly for non-Blacks (105.2, 105.4, 105.4, and 111.0 mg/dl for the background, unknown, low, and high current dioxin categories,  $p=0.613$ ). No significant findings were noted for the adjusted analysis after excluding the interaction (Table 10-36 [j]:  $p>0.35$  for each contrast).

### **Creatine Kinase (Discrete)**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The unadjusted initial dioxin analyses of discretized creatine kinase were not significant (Table 10-37 [a] and [b]:  $p=0.144$  and  $p=0.228$  for the minimal and maximal cohorts).

After adjustment for race and the age-by-degreasing chemical interaction, the adjusted relative risk was not significant for the minimal cohort (Table 10-37 [c]:  $p=0.123$ ), but was marginally less than 1 for the maximal cohort (Table 10-37 [d]: Adj. RR=0.79,  $p=0.084$ ). For the maximal cohort, the percentages of Ranch Hands with an abnormal level of creatine kinase were 5.4, 6.5, and 2.7 percent for the low, medium, and high initial dioxin categories.

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

Under the minimal assumption, the interaction between current dioxin and time since tour was marginally significant in the unadjusted analysis of discretized creatine kinase (Table 10-37 [e]:  $p=0.065$ ). The relative risk was marginally less than 1 for Ranch Hands with a later tour ( $\text{time} \leq 18.6$ : Est. RR=0.49,  $p=0.053$ ). The percentages of abnormally high levels of creatine kinase decreased with current dioxin (9.7%, 5.6%, and 0.0% for the low, medium, and high current dioxin categories) in this time stratum. By contrast, the percentages of abnormal creatine kinase values increased with dioxin for Ranch Hands with an early tour (3.4%, 4.6%, and 5.2% for the low, medium, and high current dioxin categories), although the relative risk was not significant ( $\text{time} > 18.6$ : Est. RR=1.05,  $p=0.836$ ). The current dioxin-by-time interaction was not significant in the unadjusted maximal analysis (Table 10-37 [f]:  $p=0.413$ ).

After adjustment for race and the age-by-degreasing chemical exposure interaction, the current dioxin-by-time interaction was not significant under either assumption (Table 10-37 [g] and [h]:  $p=0.119$  and  $p=0.677$  for the minimal and maximal assumptions). For the minimal cohort, the relative risk of an abnormal creatine kinase level remained marginally less than 1 for Ranch Hands with a later tour (Adj. RR=0.48,  $p=0.070$ ).

#### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis found a marginally significant difference among the prevalences of abnormally high levels of creatine kinase (Table 10-37 [i]: 7.8%, 5.3%, 5.2%, and 3.8% for the background, unknown, low, and high current dioxin categories,  $p=0.099$ ). The estimated relative risk was marginally less than 1 for the high versus background contrast (Est. RR=0.46, 95% C.I.: [0.21, 1.02],  $p=0.057$ ).

The adjusted analysis revealed a significant current dioxin-by-race interaction (Table 10-37 [j]:  $p=0.011$ ). Stratifying by race, a significant difference among prevalence rates was



**TABLE 10-37.**  
**Analysis of Creatine Kinase**  
**(Discrete)**

Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=517)	Low	130	7.7	0.77 (0.53,1.11)	0.144
	Medium	257	4.7		
	High	130	3.1		
b) Maximal (n=737)	Low	184	5.4	0.86 (0.67,1.11)	0.228
	Medium	368	6.5		
	High	185	2.7		
Ranch Hands - Log <sub>2</sub> (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
c) Minimal (n=517)	0.74 (0.49,1.10)		0.123	RACE (p<0.001) AGE*DC (p<0.001)	
d) Maximal (n=737)	0.79 (0.60,1.04)		0.084	RACE (p<0.001) AGE*DC (p<0.001)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.  
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

**TABLE 10-37. (Continued)**

**Analysis of Creatine Kinase  
(Discrete)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	9.7 (72)	5.6 (126)	0.0 (53)	0.49 (0.24,1.01)	0.065 <sup>b</sup> 0.053 <sup>c</sup>
	>18.6	3.4 (58)	4.6 (131)	5.2 (77)	1.05 (0.67,1.64)	0.836 <sup>c</sup>
f) Maximal (n=737)	≤18.6	4.8 (105)	7.4 (189)	2.4 (82)	0.77 (0.51,1.16)	0.413 <sup>b</sup> 0.210 <sup>c</sup>
	>18.6	6.3 (79)	4.5 (178)	4.8 (104)	0.96 (0.68,1.35)	0.813 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g) Minimal (n=517)	≤18.6	0.48 (0.22,1.06)		0.119 <sup>b</sup> 0.070 <sup>c</sup>	RACE (p<0.001) AGE*DC (p<0.001)	
	>18.6	0.98 (0.58,1.64)		0.925 <sup>c</sup>		
h) Maximal (n=737)	≤18.6	0.74 (0.47,1.15)		0.677 <sup>b</sup> 0.182 <sup>c</sup>	RACE (p<0.001) AGE*DC (p<0.001)	
	>18.6	0.84 (0.57,1.23)		0.363 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

**TABLE 10-37. (Continued)**

**Analysis of Creatine Kinase  
(Discrete)**

**i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	7.8	All Categories		0.099
Unknown	341	5.3	Unknown vs. Background	0.66 (0.38,1.13)	0.127
Low	193	5.2	Low vs. Background	0.64 (0.32,1.28)	0.209
High	186	3.8	High vs. Background	0.46 (0.21,1.02)	0.057
Total	1,499				

**j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted**

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.154**	DXCAT*RACE (p=0.011) ALC (p=0.135)
Unknown	339	Unknown vs. Background	0.76 (0.43,1.35)**	0.345**	AGE*DC (p<0.001)
Low	191	Low vs. Background	0.56 (0.26,1.20)**	0.134**	
High	185	High vs. Background	0.48 (0.21,1.10)**	0.083**	
Total	1,494				

\*\*Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

noted for Blacks (Appendix Table I-1: 54.3%, 25.0%, 0.0%, and 25.0% for the background, unknown, low, and high current dioxin categories,  $p=0.001$ ), but not for non-Blacks (4.9%, 4.6%, 4.9%, and 2.8% for the corresponding current dioxin categories,  $p=0.664$ ). After excluding the interaction, the overall contrast became nonsignificant ( $p=0.154$ ), although the relative risk for the high versus background contrast remained marginally less than 1 (Table 10-37 [j]: Adj. RR=0.48, 95% C.I.: [0.21,1.10],  $p=0.083$ ).

## **Longitudinal Analysis**

### ***Laboratory Examination Variables***

For the gastrointestinal assessment, longitudinal analyses were conducted to evaluate the association between various measures of dioxin (initial dioxin, current dioxin and time since tour, categorized current dioxin) and the change between the 1982 Baseline examination and the 1987 examination in levels of AST, ALT, and GGT. For a specific longitudinal analysis of AST, ALT, or GGT (e.g., minimal assumption, initial dioxin analysis), the left side of each subpanel of a table provides the means and sample sizes for participants with laboratory values at each examination. Based on the difference between 1987 and 1982 laboratory values, the right side of each subpanel presents slopes, standard errors, and associated p-values (for models using initial dioxin or models using current dioxin and time), or differences of examination mean changes, 95 percent confidence intervals, and associated p-values (for models using categorized current dioxin). The reported statistics for all three examinations are presented for all participants who were compliant at both the 1982 and 1987 examinations. Tables 10-38, 10-39, and 10-40 present the results of the longitudinal analyses of AST, ALT, and GGT.

#### **AST (Continuous)**

##### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

For both the minimal and the maximal cohorts, the longitudinal analyses did not display a significant association between initial dioxin and the change in AST between the 1982 and 1987 examinations (Table 10-38 [a] and [b]:  $p=0.475$  and  $p=0.245$ , respectively).

##### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The longitudinal analysis of the change in AST did not detect a significant current dioxin-by-time since tour interaction for either the minimal or the maximal cohorts (Table 10-38 [c] and [d]:  $p=0.870$  and  $p=0.723$ ).

##### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The change in mean levels of AST between the 1982 Baseline examination and the 1987 examination did not differ significantly among the four current dioxin categories (Table 10-38 [e]:  $p=0.268$ ).

**TABLE 10-38.**  
**Longitudinal Analysis of AST (U/L)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin)</b>						
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>Mean<sup>a</sup>/(n) Examination</b>			<b>Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>
		<b>1982</b>	<b>1985</b>	<b>1987</b>		
a) Minimal (R <sup>2</sup> =0.001)	Low	33.9	35.3	26.9	-0.0080 (0.0112)	0.475
		(124)	(121)	(124)		
	Medium	33.1	33.8	25.7		
		(252)	(248)	(252)		
	High	34.4	34.4	26.2		
		(123)	(121)	(123)		
b) Maximal (R <sup>2</sup> =0.002)	Low	32.0	32.6	24.9	-0.0093 (0.0080)	0.245
		(169)	(166)	(169)		
	Medium	33.2	34.4	26.3		
		(356)	(349)	(356)		
	High	34.0	34.3	26.2		
		(177)	(174)	(177)		

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on difference between natural logarithm of 1987 AST and natural logarithm of 1982 AST versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

**TABLE 10-38. (Continued)**  
**Longitudinal Analysis of AST (U/L)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time							
Assumption	Time (Yrs.)	Examination	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value
			Low	Medium	High		
c) Minimal (R <sup>2</sup> =0.002)	≤18.6	1982	33.6 (69)	31.6 (123)	34.4 (50)	-0.0120 (0.0182)	0.870 <sup>c</sup> 0.511 <sup>d</sup>
		1985	33.7 (67)	34.4 (121)	33.6 (49)		
		1987	25.6 (69)	25.2 (123)	25.0 (50)		
	>18.6	1982	35.1 (55)	34.0 (129)	34.8 (73)	-0.0081 (0.0149)	0.585 <sup>d</sup>
		1985	36.0 (54)	33.8 (127)	34.9 (72)		
		1987	28.8 (55)	26.3 (129)	26.9 (73)		
d) Maximal (R <sup>2</sup> =0.004)	≤18.6	1982	32.3 (93)	32.1 (183)	33.5 (78)	-0.0152 (0.0125)	0.723 <sup>c</sup> 0.224 <sup>d</sup>
		1985	33.0 (90)	34.0 (179)	34.1 (77)		
		1987	25.8 (93)	24.8 (183)	25.6 (78)		
	>18.6	1982	31.4 (76)	34.9 (172)	33.8 (100)	-0.0094 (0.0108)	0.388 <sup>d</sup>
		1985	31.3 (75)	35.4 (170)	34.1 (98)		
		1987	24.3 (76)	27.6 (172)	27.0 (100)		

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on difference between natural logarithm of 1987 AST and natural logarithm of 1982 AST versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: **Minimal**--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

**Maximal**--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

**TABLE 10-38. (Continued)**  
**Longitudinal Analysis of AST**  
**(Continuous)**

e) Ranch Hands and Comparisons by Current Dioxin Category							
Category	Mean <sup>a</sup> /(n) Examination			Contrast	Difference of Examination Mean Change (95% C.I.) <sup>e</sup>		p-Value <sup>f</sup>
	1982	1985	1987				
Background	33.1 (677)	33.9 (671)	25.6 (677)	All Categories			0.268
Unknown	31.3 (311)	32.4 (306)	25.0 (311)	Unknown vs. Background	1.2	--	0.109
Low	33.3 (189)	34.2 (187)	25.3 (189)	Low vs. Background	-0.5	--	0.503
High	33.7 (178)	34.1 (175)	26.4 (178)	High vs. Background	0.2	--	0.595
(R <sup>2</sup> =0.003)							

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of 1987 and 1982 examination mean changes on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

**TABLE 10-39.**  
**Longitudinal Analysis of ALT (U/L)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin)</b>						
Assumption	Initial Dioxin	Mean <sup>a</sup> /(n) Examination			Slope (Std. Error) <sup>b</sup>	p-Value
		1982	1985	1987		
a) Minimal (R <sup>2</sup> <0.001)	Low	21.8	23.7	21.2	-0.0072 (0.0176)	0.684
		(124)	(121)	(124)		
	Medium	21.2	22.9	21.5		
		(252)	(248)	(252)		
	High	23.7	24.3	23.2		
		(123)	(121)	(123)		
b) Maximal (R <sup>2</sup> =0.004)	Low	18.0	19.4	18.8	-0.0213 (0.0129)	0.099
		(169)	(166)	(169)		
	Medium	20.9	23.0	21.4		
		(356)	(349)	(356)		
	High	23.2	24.0	22.8		
		(177)	(174)	(177)		

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on difference between natural logarithm of 1987 ALT and natural logarithm of 1985 ALT versus log<sub>2</sub> dioxin.

Note: **Minimal**--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

**Maximal**--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.



**TABLE 10-39. (Continued)**  
**Longitudinal Analysis of ALT (U/L)**  
**(Continuous)**

Ranch Hands - Log <sub>2</sub> (Current Dioxin) and Time							
Assumption	Time (Yrs.)	Examination	Mean <sup>a</sup> /(n) Current Dioxin			Slope (Std. Error) <sup>b</sup>	p-Value
			Low	Medium	High		
c) Minimal (R <sup>2</sup> =0.001)	≤18.6	1982	21.9 (69)	20.2 (123)	25.0 (50)	-0.0047 (0.0288)	0.797 <sup>c</sup> 0.871 <sup>d</sup>
		1985	22.2 (67)	23.7 (121)	25.3 (49)		
		1987	20.0 (69)	21.5 (123)	22.3 (50)		
	>18.6	1982	22.6 (55)	21.1 (129)	24.2 (73)	-0.0142 (0.0235)	0.545 <sup>d</sup>
		1985	25.2 (54)	22.3 (127)	24.0 (72)		
		1987	22.7 (55)	21.5 (129)	23.8 (73)		
d) Maximal (R <sup>2</sup> =0.006)	≤18.6	1982	18.2 (93)	20.4 (183)	23.4 (78)	-0.0305 (0.0202)	0.749 <sup>c</sup> 0.132 <sup>d</sup>
		1985	19.9 (90)	22.5 (179)	24.9 (77)		
		1987	19.7 (93)	20.4 (183)	22.7 (78)		
	>18.6	1982	17.2 (76)	22.0 (172)	22.5 (100)	-0.0219 (0.0175)	0.211 <sup>d</sup>
		1985	18.3 (75)	23.9 (170)	23.3 (98)		
		1987	17.6 (76)	22.3 (172)	23.6 (100)		

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on difference between natural logarithm of 1987 ALT and natural logarithm of 1985 ALT versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

**TABLE 10-39. (Continued)**  
**Longitudinal Analysis of ALT (U/L)**  
**(Continuous)**

<b>e) Ranch Hands and Comparisons by Current Dioxin Category</b>						
<b>Current Dioxin Category</b>	<b>Mean<sup>a</sup>/(n) Examination</b>			<b>Contrast</b>	<b>Difference of Examination Mean Change (95% C.I.)<sup>e</sup></b>	<b>p-Value<sup>f</sup></b>
	<b>1982</b>	<b>1985</b>	<b>1987</b>			
Background	20.7 (677)	22.8 (671)	20.5 (677)	All Categories		0.005
Unknown	17.2 (311)	19.5 (306)	19.0 (311)	Unknown vs. Background	2.0 --	<0.001
Low	21.0 (189)	22.9 (187)	20.9 (189)	Low vs. Background	0.1 --	0.890
High	22.9 (178)	24.0 (175)	23.2 (178)	High vs. Background	0.6 --	0.508
(R <sup>2</sup> =0.010)						

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on natural logarithm scale.

<sup>f</sup>p-value is based on difference of 1987 and 1982 examination mean changes on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

**TABLE 10-40.**  
**Longitudinal Analysis of GGT (U/L)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin)</b>						
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>Mean<sup>a</sup>/(n) Examination</b>			<b>Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>
		<b>1982</b>	<b>1985</b>	<b>1987</b>		
a) Minimal (R <sup>2</sup> <0.001)	Low	44.1 (124)	37.5 (121)	35.6 (124)	0.0018 (0.0174)	0.918
	Medium	42.4 (252)	35.4 (248)	36.1 (252)		
	High	44.0 (123)	34.7 (121)	36.1 (123)		
b) Maximal (R <sup>2</sup> <0.001)	Low	33.9 (169)	27.5 (166)	28.7 (169)	-0.0065 (0.0124)	0.602
	Medium	42.4 (356)	35.7 (349)	35.6 (356)		
	High	43.2 (177)	35.1 (174)	36.1 (177)		

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on difference between natural logarithm of 1987 GGT and natural logarithm of 1982 GGT versus log<sub>2</sub> dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

**TABLE 10-40. (Continued)**  
**Longitudinal Analysis of GGT (U/L)**  
**(Continuous)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time</b>							
<b>Assumption</b>	<b>Time (Yrs.)</b>	<b>Examination</b>	<b>Mean<sup>a</sup>/(n) Current Dioxin</b>			<b>Slope (Std. Error)<sup>b</sup></b>	<b>p-Value</b>
			<b>Low</b>	<b>Medium</b>	<b>High</b>		
c) Minimal (R <sup>2</sup> <0.001)	≤18.6	1982	42.7 (69)	39.9 (123)	43.2 (50)	0.0040 (0.0285)	0.962 <sup>c</sup> 0.889 <sup>d</sup>
		1985	35.6 (67)	35.0 (121)	33.8 (49)		
		1987	33.3 (69)	35.8 (123)	33.4 (50)		
		1982	48.6 (55)	43.6 (129)	44.9 (73)	0.0022 (0.0232)	0.924 <sup>d</sup>
		1985	40.7 (54)	35.4 (127)	35.7 (72)		
		1987	39.5 (55)	36.2 (129)	37.5 (73)		
	>18.6	1982	33.5 (93)	39.9 (183)	42.4 (78)	-0.0053 (0.0195)	0.908 <sup>c</sup> 0.785 <sup>d</sup>
		1985	27.0 (90)	33.7 (179)	35.9 (77)		
		1987	28.4 (93)	33.0 (183)	36.7 (78)		
		1982	34.0 (76)	45.8 (172)	43.2 (100)	-0.0083 (0.0168)	0.623 <sup>d</sup>
		1985	27.1 (75)	38.1 (170)	35.1 (98)		
		1987	28.4 (76)	38.0 (172)	37.4 (100)		

<sup>a</sup>Transformed from natural logarithm scale.

<sup>b</sup>Slope and standard error based on difference between natural logarithm of 1987 GGT and natural logarithm of 1982 GGT versus log<sub>2</sub> dioxin.

<sup>c</sup>Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

<sup>d</sup>Test of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

**TABLE 10-40. (Continued)**  
**Longitudinal Analysis of GGT (U/L)**  
**(Continuous)**

<b>e) Ranch Hands and Comparisons by Current Dioxin Category</b>						
<b>Category</b>	<b>Mean<sup>a</sup>/(n) Examination</b>			<b>Contrast</b>	<b>Difference of Examination Mean Change (95% C.I.)<sup>e</sup></b>	<b>p-Value<sup>f</sup></b>
	<b>1982</b>	<b>1985</b>	<b>1987</b>			
Background	38.1 (677)	31.8 (671)	31.6 (677)	All Categories		0.098
Unknown	32.9 (311)	27.8 (306)	29.0 (311)	Unknown vs. Background	2.6 --	0.028
Low	42.9 (189)	34.9 (187)	35.2 (189)	Low vs. Background	-1.1 --	0.804
High	42.8 (178)	35.4 (175)	37.1 (178)	High vs. Background	0.8 --	0.208
(R <sup>2</sup> =0.005)						

<sup>a</sup>Transformed from natural logarithm scale.

<sup>e</sup>Difference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on natural logarithm scale.

<sup>f</sup>P-value is based on difference of 1987 and 1982 examination mean changes on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.

Unknown (Ranch Hands): Current Dioxin ≤10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

## **ALT (Continuous)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under the minimal assumption, the longitudinal analysis of ALT did not find a significant association between initial dioxin and the change in ALT between examinations (Table 10-39 [a]:  $p=0.684$ ). However, under the maximal assumption, the longitudinal analysis detected a marginally significant negative association between initial dioxin and the change in ALT (Table 10-39 [b]:  $p=0.099$ ). The mean level of ALT increased between 1982 and 1987 in the low (18.0 U/L to 18.8 U/L) and medium (20.9 U/L to 21.4 U/L) initial dioxin categories, but the mean level decreased in the high initial dioxin category (23.2 U/L to 22.8 U/L).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

For both the minimal and the maximal cohorts, the longitudinal analysis of the change in ALT between the 1982 Baseline examination and the 1987 examination did not detect a significant interaction between current dioxin and time since tour (Table 10-39 [c] and [d]:  $p=0.797$  and  $p=0.749$ , respectively).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The longitudinal analysis of categorized current dioxin detected a significant difference in the mean change in levels of ALT over time among the four current dioxin categories (Table 10-39 [e]:  $p=0.005$ ). The changes in the mean ALT values for the background, unknown, low, and high categories were -0.2, 1.8, -0.1, and 0.3 U/L. The unknown versus background contrast was highly significant (Table 10-39 [e]:  $p<0.001$ ); that is, the mean change in ALT values was greater for the Ranch Hands in the unknown category than for the Comparisons in the background category.

## **GGT (Continuous)**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under both the minimal and maximal assumptions, the longitudinal analyses did not find a significant association between initial dioxin and the change in GGT between the 1982 and 1987 examinations (Table 10-40 [a] and [b]:  $p=0.918$  and  $p=0.602$ , respectively).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The longitudinal analysis of the change in GGT did not detect a significant current dioxin-by-time since tour interaction for either the minimal or the maximal cohorts (Table 10-40 [c] and [d]:  $p=0.962$  and  $p=0.908$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The change in GGT over time differed marginally among the four current dioxin categories (Table 10-40 [e]:  $p=0.098$ ). The mean levels of GGT decreased between 1982 and 1987 for each current dioxin category (mean difference: -6.5, -3.9, -7.7, and -5.7 U/L for the background, unknown, low, and high current dioxin categories). The decrease between examinations in the mean GGT was significantly less in the unknown current dioxin category than in the background category ( $p=0.028$ ).

## DISCUSSION

Signs and symptoms associated with the gastrointestinal system are among those most frequently encountered in ambulatory medicine. The historical, physical examination, and laboratory parameters included in the gastrointestinal assessment are well established in clinical practice as screening tools in the outpatient investigation of digestive disorders. More definitive diagnostic studies, such as barium and endoscopic surveys of the bowel, were not included in the current study. These are rarely indicated in the initial evaluation of gastrointestinal disease except in emergency circumstances.

It is important to recognize certain limitations in relying upon data from the history and physical examination when diagnosing digestive disorders. Rather than pointing to a particular diagnosis, digestive symptoms frequently are nonspecific and intermittent. In this setting, even the best designed medical history questionnaire can be subject to error. "Ulcer" and "colitis" are diagnoses that are commonly reported but often not accurately established. In contrast, most cases of hepatitis are anicteric and escape detection. As a common target organ for situational stress, the bowel frequently gives rise to symptoms that can be severe but that are functional in nature and resolve over time. These caveats highlight the importance of the type of medical record verification conducted in the current study and, in the case of hepatitis, the need for serologic confirmation.

In contrast to some organ systems, the physical examination in gastrointestinal disease is often of limited value and can be misleading in the differential diagnosis. The ability of the examiner to detect hepatomegaly is unreliable in the obese patient. In obstructive airway disease, with hyperinflation of the lungs and flattening of the diaphragms, the liver edge may descend abnormally below the right costal margin in the absence of hepatomegaly. Even in the best circumstance, the span of the liver by palpation or percussion is often an unreliable index of liver size.

Data collected in the laboratory can provide early insight into the presence of occult liver disease even though there are limitations to the history and physical examination. The four hepatic enzymes analyzed as dependent variables (AST, ALT, GGT, and LDH) are common to most chemistry panels ordered in the outpatient setting. Present in high intracellular concentration, these enzymes are released in virtually all toxic, inflammatory, and neoplastic diseases with hepatic involvement. The hepatic enzymes are reliable laboratory markers of liver disease. GGT is considered the most sensitive and LDH, with isoenzymes derived from multiple organ systems, is the least specific.

The hepatic enzymes are used in the detection and followup of parenchymal disease. The serum alkaline phosphatase and bilirubin reflective of hepatobiliary function are used to recognize "cholestatic" or "obstructive" diseases. Though present in virtually all organ systems, the serum alkaline phosphatase in the adult population under study is of dual origin and close to a 50-50 mixture of liver- and bone-derived fractions. An elevated alkaline phosphatase is by no means diagnostic of liver disease. It may occur in a broad range of unrelated clinical conditions including drug-induced cholestasis, Paget's disease (3% of males over age 40), neoplasia with metastases to bone, and congestive heart failure.

Similarly, and pertinent to the current study, the bilirubin measurements are subject to numerous hereditary and acquired disorders unrelated to intrinsic hepatic disease. The benign hyperbilirubinemia of Gilbert's syndrome will occur in 5 percent of the population under study. Many medications, including over-the-counter preparations, have been implicated in the overproduction of bilirubin in the hemolytic reactions associated with glucose-6-phosphate dehydrogenase deficiency, which may occur in up to 15 percent of Black American males.

With reference to the current assessment, analysis of the historical and clinical examination variables revealed no evidence for any overt hepatic disease related to the current body burden of dioxin. Most of the statistically significant associations that occurred in relation to the extrapolated initial level of serum dioxin were limited to the laboratory indices. With the exceptions noted below, they were found in the continuous rather than the more clinically relevant discrete analysis. While the observed dose-response findings are not accompanied by clinical disease, they may still represent subclinical effects.

Of the historical variables analyzed, few statistically significant associations were found. There was an increased incidence of viral hepatitis related to the extrapolated initial level of serum dioxin and, in the adjusted analysis (not adjusting for occupation), the relative risk of 1.24 remained highly significant ( $p < 0.001$ ). Furthermore, Ranch Hands with the highest levels of serum dioxin ( $> 33.3$  ppt) were at significantly greater risk (Adj. RR=1.42,  $p = 0.047$ ) than Comparisons with background levels ( $< 10$  ppt).

However, these results became nonsignificant after adjustment for occupation. Pertinent to these associations are the results of testing for serologic markers for hepatitis during previous AFHS examinations. A history of hepatitis was verified in 332 of the 841 Ranch Hands (39.5%) who were fully compliant to the 1987 physical examination and had a valid dioxin result. Among the 786 Comparisons who were fully compliant to the 1987 physical examination and had a valid dioxin result less than or equal to 10 ppt, 316 (41.5%) had a verified history of hepatitis. These apparently high rates of verified hepatitis are partially the result of testing for serological markers of viral hepatitis during prior AFHS examinations. Participants found to carry markers indicating prior viral hepatitis infection were informed of their status.

Evidence of prior Hepatitis A infection was found in the serum of 240 of 841 Ranch Hands (28.5%) and 214 of 761 Comparisons (28.1%). Hepatitis B markers were confirmed to be present in 11.1 percent (93/841) of Ranch Hands and 13.7 percent (104/761) of Comparisons. These numbers are similar to the 14 percent of Vietnam veterans found to be positive by the Centers for Disease Control in the Vietnam Experience Study.

Participants with a history of hepatitis who were not found to have serological markers for Hepatitis A or B were tested for the presence of antibodies to Hepatitis C, a recently identified cause of non-A, non-B hepatitis. None of the four Ranch Hands and none of the five Comparisons in this category were found to be positive for Hepatitis C. In these nine individuals, a specific cause of the hepatitis could not be serologically determined. These data suggest that the majority of verified episodes of hepatitis were viral in nature and not misdiagnosed dioxin-related illnesses.



Dermatologic endpoints associated with porphyria cutanea tarda following TCDD exposure have been suggested but they have been reported only in industrial accidents with levels of exposure to dioxin and other chemicals far greater than would be anticipated in the current study. By history, 31.9 percent of those with the highest levels of serum dioxin reported skin bruising or patches versus 18.4 percent for background and 27.8 percent for those with low serum levels. Although neither of the dioxin-specific skin conditions was noted on physical examination, these findings are consistent with a dose-response effect that may have resolved over time.

The laboratory data examined can be divided broadly into perenchymal (serum enzymes), hepatobiliary (serum bilirubin and alkaline phosphatase), and lipid/carbohydrate indices. It is common to find isolated elevations in some but not all of the hepatic enzymes studied when evaluating occult or low grade liver disease. Among the enzymes examined, the GGT is considered the most sensitive. By discrete and continuous analyses, it showed the strongest positive association, particularly with the extrapolated initial level of serum dioxin. In the Ranch Hand versus the Comparison analysis, GGT was the only enzyme that showed statistically significant differences in both the continuous and discrete forms. There was no apparent association between the body burden of dioxin and elevations in the urinary d-glucaric acid, which is felt by many people to be a highly sensitive marker of dioxin-induced hepatic disease.

Serum alkaline phosphatase in its continuous form was significantly associated with the extrapolated initial body burden of dioxin. By the more clinically relevant discrete analysis, however, there was no evidence of a significant dose-response effect. In contrast, both the unadjusted and adjusted analyses of total bilirubin revealed a direct opposite effect with a decreasing percentage of abnormal results in participants with higher levels of initial dioxin.

In relation to other laboratory variables, the lipid indices analyzed had the highest number of statistically significant positive associations with the body burden of dioxin. In a pattern consistent with a dose-response effect, a highly significant ( $p < 0.001$ ) association was found between the extrapolated initial serum dioxin and triglyceride levels. A significant association was noted in the discrete analysis as well. The interpretation of these results must consider the disproportionate increase in obesity in Ranch Hands with high versus those with low levels of serum dioxin (29.0% versus 12.4%; see Chapter 6, General Health Assessment).

In conclusion, the data analyzed in the current study suggest the presence of a subclinical effect on lipid metabolism, possibly related to the elevations previously seen in percent body fat. Several strongly positive associations were found between dioxin levels and triglycerides. This is not surprising since triglycerides are sensitive to weight and more specifically to percent body fat. Further longitudinal study into the pharmacokinetics of dioxin in lean versus obese individuals will be important toward understanding the clinical significance of the associations between all weight sensitive indices with serum levels of dioxin.

## **SUMMARY**

Table 10-41 summarizes the results of the initial dioxin analyses (model 1) for the variables analyzed in the gastrointestinal assessment. Table 10-42 presents the results of the current dioxin and time since tour analyses (model 2), and Table 10-43 summarizes the categorized current dioxin analyses (model 3). Table 10-44 lists the numerous dioxin-by-covariate interactions that were encountered in the adjusted analyses of the laboratory variables.

### **Questionnaire Variables**

Information collected at the 1987 health interview was combined with information collected at the 1982 and 1985 examinations, verified, and grouped into eight categories of liver disorders for analysis: viral hepatitis, acute and subacute necrosis of the liver, chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related were analyzed separately), liver abscess and sequelae of chronic liver disease, other disorders of the liver, jaundice (unspecified, not of the newborn), and hepatomegaly. No Ranch Hands had necrosis of the liver or liver abscess and sequelae of chronic liver disease. Three Comparisons had necrosis of the liver and one had liver abscess and sequelae of chronic liver disease. Verified histories of ulcers and of skin bruises, patches, or sensitivity also were analyzed.

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Adjusting for age and race, initial dioxin was associated significantly with an increased incidence of hepatitis under the minimal and maximal assumptions. However, this appears to be a spurious relationship that was due to the confounding effect of occupation. The incidence of hepatitis differed significantly among occupations (enlisted personnel had a higher incidence than officers). The relative risk of hepatitis became nonsignificant after adjusting for occupation. Under the maximal assumption, there was a marginally significant increased risk for the category of other liver disorders. None of the other liver conditions, as well as ulcers and skin bruises, patches, or sensitivity was significantly associated with initial dioxin.

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The current dioxin and time since tour analyses did not find a significant interaction between current dioxin and time for any of the liver conditions or for ulcers or skin bruises, patches, or sensitivity. Under the minimal and maximal assumptions, the incidence of hepatitis was associated significantly with current dioxin for Ranch Hands with a later tour when adjusting for age and race. However, these findings became nonsignificant when occupation was added to the model.

#### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of hepatitis differed significantly among the four current dioxin categories when adjusting for age and race, with a significant increased risk in the high current dioxin category relative to the background category. Comparable to the hepatitis results for model 1 and model 2 analyses, these findings became nonsignificant after adjusting for the confounding effect of occupation.

TABLE 10-41.

**Summary of Initial Dioxin Analyses for Gastrointestinal Variables  
Based on Minimal and Maximal Assumptions  
(Ranch Hands Only)**

Variable	Unadjusted		Adjusted	
	Minimal	Maximal	Minimal	Maximal
<b>Questionnaire</b>				
Viral Hepatitis (D)	NS	NS*	+0.028	+<0.001
Viral Hepatitis <sup>a</sup> (D)	- -	- -	NS	NS
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	ns	ns	ns	ns
Chronic Liver Disease and Cirrhosis (Nonalcohol- Related) (D)	ns	ns	ns	ns
Other Disorders of the Liver (D)	NS	NS*	NS	NS*
Jaundice (Unspecified) (D)	NS	ns	NS	ns
Hepatomegaly (D)	ns	NS	NS	NS
Ulcer (D)	NS	NS	NS	NS
Skin Bruises, Patches, or Sensitivity (D)	NS	NS	NS	NS
<b>Physical Examination</b>				
Current Hepatomegaly (D)	ns	NS	ns	NS
<b>Laboratory</b>				
AST (C)	NS	NS	** (ns)	NS
AST (D)	NS	NS	** (ns)	** (ns)
ALT (C)	+0.039	+<0.001	NS	** (+0.005)
ALT (D)	NS	+0.031	** (NS)	** (NS*)
GGT (C)	NS	+<0.001	NS	+<0.001
GGT (D)	NS	NS*	*** (NS)	*** (+0.028)
Alkaline Phosphatase (C)	NS	+0.007	NS	+0.030
Alkaline Phosphatase (D)	NS	NS*	NS	NS
D-Glucaric Acid (C)	NS	NS*	** (NS)	NS
D-Glucaric Acid (D)	ns	ns	--	--
Total Bilirubin (C)	ns	ns	ns	** (ns)
Total Bilirubin (D)	-0.007	-0.033	-0.001	-0.014
Direct Bilirubin (C)	NS	NS*	NS	+0.038
Direct Bilirubin (D)	ns*	ns	** (ns)	** (ns)
LDH (C)	ns	NS	ns	NS
LDH (D)	ns	ns*	--	--

TABLE 10-41. (Continued)

**Summary of Initial Dioxin Analyses for Gastrointestinal Variables  
Based on Minimal and Maximal Assumptions  
(Ranch Hands Only)**

Variable	Unadjusted		Adjusted	
	Minimal	Maximal	Minimal	Maximal
Cholesterol (C)	NS	NS	+0.046	+0.041
Cholesterol (D)	ns	ns	ns	ns
HDL <sup>b</sup> (C)	ns	-<0.001	ns	*** (-<0.001)
HDL (D)	NS	NS	NS	NS
Cholesterol-HDL Ratio (C)	+0.031	+<0.001	+0.009	*** (+<0.001)
Cholesterol-HDL Ratio (D)	NS*	+<0.001	+0.004	*** (+<0.001)
Triglycerides (C)	NS*	+<0.001	+0.040	+<0.001
Triglycerides (D)	+0.021	+0.004	+0.026	+0.005
Creatine Kinase (C)	ns	ns	** (ns)	** (ns)
Creatine Kinase (D)	ns	ns	ns	ns*

<sup>a</sup>Adjusted for age and occupation. Appendix Table I-2 presents a detailed description of this analysis.

<sup>b</sup>Negative slope considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

-: Relative risk less than 1.00 for discrete analysis; slope negative for continuous analysis.

--: Analysis not performed due to the sparse number of abnormalities.

NS/ns: Not significant ( $p > 0.10$ ).

NS\*/ns\*: Marginally significant ( $0.05 < p \leq 0.10$ ).

\*\* (NS)/\*\* (ns):  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\* (NS\*):  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $0.01 < p \leq 0.05$ ); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\* (...):  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $0.01 < p \leq 0.05$ ); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\*\* (NS):  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $p \leq 0.01$ ); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\*\* (...):  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $p \leq 0.01$ ); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.

Note: P-value given if  $p \leq 0.05$ .

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

TABLE 10-42.

**Summary of Current Dioxin and Time Analyses for Gastrointestinal  
Variables Based on Minimal and Maximal Assumptions  
(Ranch Hands Only)**

Variable	Unadjusted					
	Minimal			Maximal		
	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
<b>Questionnaire</b>						
Viral Hepatitis (D)	ns	NS	ns	ns	NS	NS
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	ns	NS	ns	ns	NS	ns
Chronic Liver Disease and Cirrhosis (Nonalcohol- Related) (D)	--	ns	--	--	ns	--
Other Disorders of the Liver (D)	ns	NS	NS	ns	NS	NS
Jaundice (Unspecified) (D)	NS	ns	NS	ns	NS	ns
Hepatomegaly (D)	NS	ns	ns	ns	NS	ns
Ulcer (D)	ns	NS	NS	ns	NS	NS
Skin Bruises, Patches, or Sensitivity (D)	ns	NS	ns	ns	NS	NS
<b>Physical Examination</b>						
Current Hepatomegaly (D)	ns	ns	ns	ns	NS	NS
<b>Laboratory</b>						
AST (C)	ns	NS	ns	NS	NS	NS
AST (D)	NS	ns	NS	NS	ns	NS
ALT (C)	ns	NS*	NS	ns	+0.022	+0.010
ALT (D)	ns	NS*	NS	ns	+0.028	NS
GGT (C)	ns	NS	NS	ns	+0.011	+0.048
GGT (D)	ns	NS	NS	ns	NS	NS
Alkaline Phosphatase (C)	NS	NS	NS	ns	NS*	NS
Alkaline Phosphatase (D)	NS	ns	NS	NS	NS	+0.046
D-Glucaric Acid (C)	NS	NS	NS	ns	NS	NS
D-Glucaric Acid (D)	--	--	--	ns	ns	ns
Total Bilirubin (C)	NS	ns	NS	NS	ns	NS
Total Bilirubin (D)	ns	ns	-0.045	NS	ns	ns
Direct Bilirubin (C)	NS	NS	NS	NS	NS	NS
Direct Bilirubin (D)	NS	ns	ns	ns	ns	ns

TABLE 10-42. (Continued)

**Summary of Current Dioxin and Time Analyses for Gastrointestinal  
Variables Based on Minimal and Maximal Assumptions  
(Ranch Hands Only)**

Variable	Unadjusted					
	Minimal			Maximal		
	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
LDH (C)	NS	ns	ns	NS	ns	ns
LDH (D)	--	--	--	--	ns	--
Cholesterol (C)	NS*	ns	+0.024	NS	NS	NS
Cholesterol (D)	NS	ns	NS	NS	ns	ns
HDL <sup>a</sup> (C)	ns	ns	ns	NS	-0.008	-0.014
HDL (D)	ns	NS	NS	NS	ns	NS
Cholesterol-HDL Ratio (C)	NS	NS	+0.023	NS	+0.015	+0.001
Cholesterol-HDL Ratio (D)	NS	ns	+0.039	NS	NS	+0.005
Triglycerides (C)	ns	NS	NS	ns*	+<0.001	NS*
Triglycerides (D)	ns	NS	NS*	ns	+0.045	+0.044
Creatine Kinase (C)	NS	ns	NS	ns	NS	ns
Creatine Kinase (D)	NS*	ns*	NS	NS	ns	ns

<sup>a</sup>Negative slope considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: <18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

-: <18.6 and >18.6: Relative risk less than 1.00 for discrete analysis; slope negative for continuous analysis.

--: Analysis not performed due to the sparse number of abnormalities.

NS/ns: Not significant ( $p > 0.10$ ).

NS\*/ns\*: Marginally significant ( $0.05 \leq p < 0.10$ ).

Note: P-value given if  $p \leq 0.05$ .

C\*T: Log<sub>2</sub> (current dioxin)-by-time interaction hypothesis test.

≤18.6: Log<sub>2</sub> (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.

>18.6: Log<sub>2</sub> (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.

A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis.

**TABLE 10-42. (Continued)**

**Summary of Current Dioxin and Time Analyses for Gastrointestinal Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)**

Variable	Adjusted					
	Minimal			Maximal		
	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
<b>Questionnaire</b>						
Viral Hepatitis (D)	ns	+0.046	NS	ns	+0.002	NS*
Viral Hepatitis <sup>a</sup> (D)	ns	NS	ns	ns	NS	ns
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	ns	NS	ns*	ns	NS	ns*
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related) (D)	--	--	--	--	--	--
Other Disorders of the Liver (D)	ns	NS	NS	ns	NS	NS
Jaundice (Unspecified) (D)	NS	NS	NS	ns	NS	ns
Hepatomegaly (D)	ns	NS	NS	ns	NS*	NS
Ulcer (D)	ns	NS	NS	ns	NS	NS
Skin Bruises, Patches, or Sensitivity (D)	ns	NS	NS	ns	NS	NS
<b>Physical Examination</b>						
Current Hepatomegaly (D)	ns	NS	NS	ns	NS	NS
<b>Laboratory</b>						
AST (C)	ns	ns	ns	****	****	****
AST (D)	NS	ns	ns	NS	ns	ns
ALT (C)	ns	NS	NS	** (ns)	** (NS*)	** (NS*)
ALT (D)	ns	NS	ns	ns	NS*	NS
GGT (C)	ns	NS	NS	ns	+0.003	NS*
GGT (D)	ns	NS	ns	ns	NS*	NS
Alkaline Phosphatase (C)	** (NS)	** (NS)	** (NS)	** (ns)	** (NS*)	** (NS)
Alkaline Phosphatase (D)	NS	ns	NS	NS	NS	+0.046
D-Glucaric Acid (C)	NS	NS	NS	ns	NS	NS
D-Glucaric Acid (D)	--	--	--	--	--	--
Total Bilirubin (C)	NS	ns	NS	NS	ns	NS
Total Bilirubin (D)	ns	ns	-0.008	ns	ns	ns*
Direct Bilirubin (C)	NS	NS	NS	ns	NS	NS
Direct Bilirubin (D)	** (NS)	** (ns)	** (ns)	ns	NS	ns

TABLE 10-42. (Continued)

**Summary of Current Dioxin and Time Analyses for Gastrointestinal  
Variables Based on Minimal and Maximal Assumptions  
(Ranch Hands Only)**

Variable	Adjusted					
	Minimal			Maximal		
	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
LDH (C)	NS	ns	ns	NS	ns	ns
LDH (D)	--	--	--	--	--	--
Cholesterol (C)	+0.049	NS	+0.002	** (NS)	** (NS)	** (+0.030)
Cholesterol (D)	****	****	****	NS	ns	ns
HDL <sup>b</sup> (C)	** (ns)	** (ns)	** (ns)	NS	-0.027	-0.042
HDL (D)	ns	NS	NS	NS	ns	NS
Cholesterol-HDL Ratio (C)	** (NS)	** (NS)	** (+0.009)	NS	+0.008	+<0.001
Cholesterol-HDL Ratio (D)	** (NS)	** (NS)	** (+0.003)	NS	NS	+0.001
Triglycerides (C)	ns	NS	NS	ns	+<0.001	+0.045
Triglycerides (D)	NS	NS	NS*	ns	+0.050	NS*
Creatine Kinase (C)	NS	ns	NS	ns	NS	ns
Creatine Kinase (D)	NS	ns*	ns	NS	ns	ns

<sup>a</sup>Adjusted for age and occupation. Appendix Table I-1 presents a detailed description of this analysis.

<sup>b</sup>Negative slope considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: C\*T: Slope for ≤18.6 category less than slope for >18.6 category.

≤18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

-: ≤18.6 and >18.6: Relative risk less than 1.00 for discrete analysis; slope negative for continuous analysis.

--: Analysis not performed due to the sparse number of abnormalities.

NS/ns: Not significant ( $p > 0.10$ ).

NS\*/ns\*: Marginally significant ( $0.05 < p \leq 0.10$ ).

\*\* (NS)/\*\* (ns): Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction ( $0.05 < p \leq 0.10$ ); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\* (NS\*): Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction ( $0.05 < p \leq 0.10$ ); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\* (...): Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction ( $0.05 < p \leq 0.10$ ); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\*\*\*: Log<sub>2</sub> (current dioxin)-by-time-by-covariate interaction ( $p \leq 0.01$ ); refer to Appendix Table I-1 for a detailed description of this interaction.

Note: P-value given if  $p \leq 0.05$ .

C\*T: Log<sub>2</sub> (current dioxin)-by-time interaction hypothesis test.

≤18.6: Log<sub>2</sub> (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.

>18.6: Log<sub>2</sub> (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.

A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category,

relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns"

denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis.



TABLE 10-43.

**Summary of Categorized Current Dioxin Analyses for  
Gastrointestinal Variables  
(Ranch Hands and Comparisons)**

Variable	All	Unadjusted		
		Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Viral Hepatitis (D)	NS	ns*	ns	NS
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	NS	NS	ns	NS
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related) (D)	NS	ns	NS	ns
Other Disorders of the Liver (D)	NS*	ns	NS	+0.036
Jaundice (D)	NS*	NS	-0.042	ns
Hepatomegaly (D)	NS	ns	ns	NS
Ulcer (D)	NS	NS	ns	NS
Skin Bruises, Patches, or Sensitivity (D)	<0.001	+0.005	+0.004	+<0.001
Physical Examination				
Current Hepatomegaly (D)	NS*	-0.036	NS	NS
Laboratory				
AST (C)	NS	ns	ns	NS
AST (D)	NS	ns	ns	NS
ALT (C)	<0.001	-0.011	NS	+0.006
ALT (D)	NS	ns	NS	NS
GGT (C)	<0.001	-0.009	NS*	+0.007
GGT (D)	0.047	ns	NS*	+0.025
Alkaline Phosphatase (C)	NS*	NS	+0.041	+0.036
Alkaline Phosphatase (D)	NS	ns	ns	NS
D-Glucaric Acid (C)	NS	ns	NS	NS
D-Glucaric Acid (D)	NS	NS	ns	NS
Total Bilirubin (C)	NS	ns	ns	ns
Total Bilirubin (D)	0.048	ns	NS	-0.050
Direct Bilirubin (C)	NS	ns	NS	+0.025
Direct Bilirubin (D)	NS	ns	NS	ns

TABLE 10-43. (Continued)

**Summary of Categorized Current Dioxin Analyses for  
Gastrointestinal Variables  
(Ranch Hands and Comparisons)**

Variable	Unadjusted			
	All	Unknown versus Background	Low versus Background	High versus Background
LDH (C)	NS	ns	ns	NS
LDH (D)	NS	ns	ns	ns
Cholesterol (C)	NS	NS	NS	NS*
Cholesterol (D)	NS	+0.022	NS	NS
HDL <sup>a</sup> (C)	<0.001	+<0.001	ns	-0.031
HDL (D)	NS	ns	NS	NS
Cholesterol-HDL Ratio (C)	<0.001	-0.002	NS*	+0.003
Cholesterol-HDL Ratio (D)	0.021	ns*	NS	NS
Triglycerides (C)	<0.001	-0.005	+<0.001	+0.004
Triglycerides (D)	<0.001	ns	+0.045	+0.002
Creatine Kinase (C)	NS	ns	ns	NS
Creatine Kinase (D)	NS*	ns	ns	ns*

<sup>a</sup>Negative difference considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.

-: Relative risk less than 1.00 for discrete analysis; difference in means negative for continuous analysis.

NS/ns: Not significant ( $p > 0.10$ ).

NS\*/ns\*: Marginally significant ( $0.05 < p \leq 0.10$ ).

Note: P-value given if  $p \leq 0.05$ .

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

TABLE 10-43. (Continued)

**Summary of Categorized Current Dioxin Analyses for  
Gastrointestinal Variables  
(Ranch Hands and Comparisons)**

Variable	All	Adjusted		
		Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Viral Hepatitis (D)	0.022	ns*	ns	+0.047
Viral Hepatitis <sup>a</sup> (D)	NS	NS	ns	NS
Chronic Liver Disease and Cirrhosis (Alcohol- Related) (D)	NS	NS	ns	NS
Chronic Liver Disease and Cirrhosis (Nonalcohol- Related) (D)	NS	NS	NS	- -
Other Disorders of the Liver (D)	NS*	ns	NS	+0.038
Jaundice (D)	0.014	NS	- -	ns
Hepatomegaly (D)	NS	ns	ns	NS
Ulcer (D)	NS	NS	ns	NS
Skin Bruises, Patches, or Sensitivity (D)	<0.001	+0.005	+0.004	+<0.001
Physical Examination				
Current Hepatomegaly (D)	0.006	- -	NS	NS
Laboratory				
AST (C)	NS	ns	ns	NS
AST (D)	NS	NS	ns	NS
ALT (C)	** (0.012)	** (ns*)	** (NS)	** (+0.035)
ALT (D)	NS	ns	NS	NS
GGT (C)	<0.001	-0.017	+0.043	+0.001
GGT (D)	** (0.033)	** (ns)	** (+0.039)	** (+0.018)
Alkaline Phosphatase (C)	NS*	NS	NS*	+0.044
Alkaline Phosphatase (D)	NS	ns	ns	NS
D-Glucaric Acid (C)	NS	ns	NS	NS
D-Glucaric Acid (D)	- -	- -	- -	- -
Total Bilirubin (C)	NS	ns	ns	ns
Total Bilirubin (D)	0.018	ns	NS	-0.030
Direct Bilirubin (C)	*** (NS*)	*** (ns)	*** (NS)	*** (+0.018)
Direct Bilirubin (D)	NS	ns	NS	ns

TABLE 10-43. (Continued)

**Summary of Categorized Current Dioxin Analyses for  
Gastrointestinal Variables  
(Ranch Hands and Comparisons)**

Variable	All	Adjusted		
		Unknown versus Background	Low versus Background	High versus Background
LDH (C)	NS	ns	ns	NS
LDH (D)	--	--	--	--
Cholesterol (C)	NS	NS	NS	+0.038
Cholesterol (D)	NS	+0.018	NS	NS
HDL <sup>b</sup> (C)	** (<0.001)	** (+<0.001)	** (ns)	** (ns)
HDL (D)	** (NS)	** (NS)	** (NS)	** (NS)
Cholesterol-HDL Ratio (C)	<0.001	-<0.001	NS	+0.003
Cholesterol-HDL Ratio (D)	0.023	ns*	NS	NS*
Triglycerides (C)	** (<0.001)	** (-0.004)	** (+<0.001)	** (+0.002)
Triglycerides (D)	** (<0.001)	** (ns*)	** (+0.045)	** (+0.001)
Creatine Kinase (C)	** (NS)	** (ns)	** (ns)	** (NS)
Creatine Kinase (D)	** (NS)	** (ns)	** (ns)	** (ns*)

<sup>a</sup>Adjusted for age and occupation. Appendix Table I-2 presents a detailed description of this analysis.

<sup>b</sup>Negative difference considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.

-: Relative risk less than 1.00 for discrete analysis; difference in means negative for continuous analysis.

--: Analysis not performed due to the sparse number of abnormalities.

NS/ns: Not significant ( $p > 0.10$ ).

NS\*/ns\*: Marginally significant ( $0.05 < p \leq 0.10$ ).

\*\* (NS)/\*\* (ns): Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\* (ns\*): Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\* (...): Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\*\* (NS)/\*\*\* (ns): Categorized current dioxin-by-covariate interaction ( $p \leq 0.01$ ); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\*\* (NS\*): Categorized current dioxin-by-covariate interaction ( $p \leq 0.01$ ); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.

\*\*\* (...): Categorized current dioxin-by-covariate interaction ( $p \leq 0.01$ ); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.

Note: P-value given if  $p \leq 0.05$ .

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

**TABLE 10-44.**

**Summary of Dioxin-by-Covariate Interactions from Adjusted Analyses of Gastrointestinal Variables**

Variable	Assumption	Covariate
<b>Model 1: Log<sub>2</sub> (Initial Dioxin)</b>		
AST (C)	Minimal	DC
AST (D)	Minimal	RACE, DC
AST (D)	Maximal	DC
ALT (C)	Maximal	AGE
ALT (D)	Minimal	DC
ALT (D)	Maximal	ALC
GGT (D)	Minimal	RACE, DC
GGT (D)	Maximal	DC
D-Glucaric Acid (C)	Minimal	RACE
Total Bilirubin (C)	Maximal	RACE
Direct Bilirubin (D)	Minimal	IC
Direct Bilirubin (D)	Maximal	IC
HDL (C)	Maximal	DC
Cholesterol-HDL Ratio (C)	Maximal	DC
Cholesterol-HDL Ratio (D)	Maximal	AGE, DC
Creatine Kinase (C)	Minimal	AGE
Creatine Kinase (C)	Maximal	AGE
<b>Model 2: Log<sub>2</sub> (Current Dioxin) and Time</b>		
AST (C)	Maximal	ALC
ALT (C)	Maximal	ALC
Alkaline Phosphatase (C)	Minimal	LWINE
Alkaline Phosphatase (C)	Maximal	RACE, WINE
Direct Bilirubin (D)	Minimal	DC
Cholesterol (C)	Maximal	DRKYR
Cholesterol (D)	Minimal	IC
HDL (C)	Minimal	IC
Cholesterol-HDL Ratio (C)	Minimal	IC
Cholesterol-HDL Ratio (D)	Minimal	IC
<b>Model 3: Ranch Hands and Comparisons by Current Dioxin Category</b>		
ALT (C)	--	DRKYR
GGT (D)	--	DC
Direct Bilirubin (C)	--	RACE
HDL (C)	--	DRKYR
HDL (D)	--	DC
Triglycerides (C)	--	ALC
Triglycerides (D)	--	ALC
Creatine Kinase (C)	--	RACE
Creatine Kinase (D)	--	RACE

C: Continuous analysis.

D: Discrete analysis.

The overall contrast was marginally significant for the category of other liver disorders in the adjusted analysis. For this variable, the relative risk for Ranch Hands with the highest current levels of dioxin (>33.3 ppt) was significantly greater than 1.

For jaundice, the unadjusted analyses found that the incidence of jaundice differed marginally among the current dioxin categories, but this was due to a significantly decreased incidence in the low current dioxin category, relative to the background category. Although the model 1 and model 2 analyses for skin bruises, patches, or sensitivity were not significant, the categorized current dioxin analyses found a highly significant increase in the incidence of skin bruises, patches, or sensitivity in each of the three Ranch Hand current dioxin categories relative to the background incidence. The categorized current dioxin analyses were not significant for the other questionnaire variables.

### **Physical Examination Variable**

The initial dioxin analyses and the current dioxin and time since tour analyses did not reveal any significant findings in hepatomegaly diagnosed at the 1987 physical examination. The unadjusted categorized current dioxin analysis showed a marginally significant difference in the prevalence of hepatomegaly among current dioxin categories, but the only significant Ranch Hand versus background contrast was a decreased risk in the unknown category.

### **Laboratory Variables**

The gastrointestinal assessment analyzed 13 laboratory variables (AST, ALT, GGT, alkaline phosphatase, d-glucuric acid, total bilirubin, direct bilirubin, LDH, cholesterol, HDL, cholesterol-HDL ratio, triglycerides, and creatine kinase). The only significant laboratory finding from the previous results of the 1987 examination was that the Ranch Hands had a higher mean alkaline phosphatase than the Comparisons.

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under the minimal assumption, the adjusted initial dioxin analyses detected significant positive associations with cholesterol (continuous), the cholesterol-HDL ratio (continuous and discrete), and triglycerides (continuous and discrete). They also found a significant decreased risk of abnormally high levels of total bilirubin. In addition to these significant findings, the adjusted maximal analyses also found significant positive associations between initial dioxin and ALT (continuous), GGT (continuous and discrete), alkaline phosphatase (continuous), and direct bilirubin (continuous). The adjusted maximal analyses also showed a significant negative relationship between initial dioxin and HDL (continuous) and a marginally significant decreased risk of abnormally high levels of creatine kinase.

The adjusted analyses frequently revealed initial dioxin-by-covariate interactions. In most instances, the covariate was either age, race, or degreasing chemical exposure. With degreasing chemical exposure, stratified analyses found significant or marginally significant increased risks of abnormally high levels of AST (minimal and maximal), ALT (minimal), GGT (minimal and maximal), and the cholesterol-HDL ratio (maximal) for Ranch Hands who had never been exposed to degreasing chemicals. In addition, the association between initial dioxin and the cholesterol-HDL ratio in its continuous form was significant for these Ranch Hands. This pattern is puzzling since it is counter to any hypothesized synergistic effort of dioxin and degreasing chemicals. Degreasing chemicals are associated with occupation

(officers were generally not exposed to degreasing chemicals). However, additional analyses adjusting for occupation still detected significant dioxin-by-degreasing chemical interactions. The initial dioxin-by-race interactions for AST and GGT were affected by sparse data. No consistent pattern emerged from exploration of the other interactions.

Initial dioxin levels were not associated significantly with the change in levels of AST, ALT, and GGT in the longitudinal analyses.

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The association between current dioxin and the laboratory variables generally did not differ significantly between time since tour strata. The adjusted minimal analyses found a significant current dioxin-by-time interaction for cholesterol (continuous). For this analysis, the association with current dioxin was significant for Ranch Hands with an early tour, but the association was not significant for those with a later tour. The current dioxin-by-time interaction was not significant for any of the adjusted maximal analyses, although it was marginally significant in the unadjusted maximal analysis of triglycerides (continuous). Many of the adjusted analyses exhibited current dioxin-by-time-by-covariate interactions, but no consistent pattern emerged suggestive of a dioxin effect. The longitudinal analyses were not significant for AST, ALT, and GGT.

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The adjusted categorized current dioxin analyses found significant overall contrasts for ALT (continuous), GGT (continuous and discrete), total bilirubin (discrete), HDL (continuous), the cholesterol-HDL ratio (continuous and discrete), and triglycerides (continuous and discrete). There was a marginally significant overall contrast for alkaline phosphatase (continuous) and direct bilirubin (continuous). The adjusted mean levels of ALT, GGT, alkaline phosphatase, direct bilirubin, cholesterol, the cholesterol-HDL ratio, and triglycerides in the high current dioxin category were significantly more than the respective adjusted means in the background category. Relative to the background category, the adjusted analyses found that Ranch Hands in the high current dioxin category had a significant increased risk of abnormally high levels of GGT and triglycerides and a significant decreased risk of abnormally high levels of total bilirubin. The high versus background contrast also showed a marginally significant increased risk of an abnormally high cholesterol-HDL ratio and a marginally significant decreased risk of an abnormally high level of creatine kinase.

In the adjusted analyses, the low versus background contrast exhibited significant positive differences for GGT (continuous and discrete) and triglycerides (continuous and discrete). The low current dioxin category also had a marginally higher adjusted mean alkaline phosphatase than the background category. The unknown versus background contrast often displayed differences that were in the opposite direction of the high versus background contrast. For this contrast, the adjusted analyses showed significant or marginally significant negative differences for ALT (continuous), GGT (continuous), the cholesterol-HDL ratio (continuous and discrete), and triglycerides (continuous and discrete), along with significant positive differences for cholesterol (discrete) and HDL (continuous).

In many instances, the means displayed a dose-response relationship for the unknown, low, and high current dioxin categories, with the background mean falling between the unknown and high categories. A possible explanation for this consistent trend was that it was due to an occupational difference among Ranch Hand categories (most officers were in the unknown category). However, the pattern persisted after performing additional analyses adjusting for occupation.

The adjusted analyses detected several categorized current dioxin-by-covariate interactions. However, no consistent pattern was noted except that both the continuous and discrete adjusted analyses of triglycerides found significant categorized current dioxin-by-current alcohol use interactions and that both the continuous and discrete adjusted analyses of creatine kinase revealed significant categorized current dioxin-by-race interactions.

The high versus background contrasts were not significant in the longitudinal analyses for AST, ALT, and GGT. The overall contrast in the longitudinal analyses was significant for ALT and marginally significant for GGT, but these findings were due to a significant unknown versus background contrast.

## CONCLUSION

The gastrointestinal assessment found statistically significant associations between dioxin and skin bruises, patches, or sensitivity, and several laboratory variables (primarily lipid related). In conjunction with findings in other chapters, these observations may represent a dioxin mediated alteration of biochemical processes.



## CHAPTER 10

### REFERENCES

1. Poiger, H., and C. Schlatter. 1986. Pharmacokinetics of 2,3,7,8-TCDD in man. *Chemosphere* 15:1489-94.
2. Kancir, C.B., C. Andersen, and A.S. Olesen. 1988. Marked hypocalcemia in a fatal poisoning with chlorinated phenoxy acid derivatives. *Clin. Toxicol.* 26:257-64.
3. Meulenbelt, J., J.H. Zwaveling, P. van Zoonen, and N.C. Notermans. 1988. Acute MCPD intoxication: Report of two cases. *Human Toxicol.* 7:289-92.
4. McNulty, W.P. 1977. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin for Rhesus monkeys: Brief report. *Bull. Environ. Contam. Toxicol.* 18:108-109.
5. Olson, J.R., M.A. Holscher, and R.A. Neal. 1980. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the golden Syrian hamster. *Toxicol. Appl. Pharmacol.* 55:67-78.
6. Palmer, J.S., and R.D. Radeleff. 1964. The toxicologic effects of certain fungicides and herbicides on sheep and cattle. *Ann. N.Y. Acad. Sci.* 11:729-36.
7. Goldstein, J.A., P. Hickman, H. Bergman, and J.G. Vos. 1973. Hepatic porphyria induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in the mouse. *Res. Commun. Chem. Pathol. Pharmacol.* 6:919.
8. Madhukar, B.V., and F. Matsumura. 1981. Difference in the nature of induction of mixed-function oxidase systems of the rat liver among phenobarbital, DDT, 3-methylcholanthrene, and TCDD. *Toxicol. Appl. Pharmacol.* 61:110-18.
9. Piper, W.N., R.Q. Rose, and P.J. Gehring. 1973. Excretion and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. *Environ. Health Perspect.* 5:241-44.
10. Allen, J.R., J.P. Van Miller, and D.H. Norback. 1977. Tissue distribution, excretion, and biological effects of (<sup>14</sup>C)tetrachlorodibenzo-p-dioxin in rats. *Food Cosmet. Toxicol.* 15:401-10.
11. Tsuda, S., A. Rosenberg, and T. Nakatsugawa. 1988. Translobular uptake patterns of environmental toxicants in the rat liver. *Bull. Environ. Contam. Toxicol.* 40:410-17.
12. Lakshmanan, M.R., B.S. Campbell, S.J. Chirtel, N. Ekarohita, and M. Ezekiel. 1986. Studies on the mechanism of absorption and distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. *J. Pharmacol. Exp. Ther.* 239:673-77.
13. Gasiewicz, T., and R.A. Neal. 1979. 2,3,7,8-tetrachlorodibenzo-p-dioxin tissue distribution, excretion, and effects on clinical chemical parameters in guinea pigs. *Toxicol. Appl. Pharmacol.* 51:329-40.
14. Gehring, P.J., and J.E. Betso. 1978. Phenoxy acids: effects and fate in mammals. *Ecol. Bull.* 27:122-33.
15. Brooks, A.L., S.W. Jordan, K.K. Bose, J. Smith, and D.C. Allison. 1988. The cytogenetic and hepatotoxic effects of dioxin on mouse liver cells. *Cell Biol. Toxicol.* 4:31-40.
16. U.S. Environmental Protection Agency. 1984. Health assessment document for polychlorinated dibenzo-p-dioxins. Cincinnati, Ohio: EPA.

17. Brooks, A.L., S.W. Jordan, K.K. Bose, J. Smith, and D.C. Allison. 1988. The cytogenetic and hepatotoxic effects of dioxin on mouse liver cells. *Cell. Biol. Toxicol.* 4:31-40.
18. Pohjanvirta, R., R. Juvonen, S. Karen-Lampi, H. Raunio, and J. Tuomisto. 1988. Hepatic Ah-receptor levels and the effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on hepatic microsomal monooxygenase activities in a TCDD-susceptible and resistant rat strain. *Toxicol. Appl. Pharmacol.* 92:131-40.
19. Poland, A., and J.C. Knutson. 1982. 2,3,7,8-tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons: Examination of the mechanism of toxicity. *Annual Review Pharmacology Toxicology* 22:517-54.
20. Sloop, T.C., and G.W. Lucier. 1987. Dose-dependent elevation of Ah receptor binding by TCDD in rat liver. *Toxicol. Appl. Pharmacol.* 88:329-37.
21. Denison, M.S., L.M. Vella, and A.B. Okey. 1986. Structure and function of the Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J. Biol. Chem.* 261:3987-95.
22. Fernandez, N., M. Roy, and P. Lesca. 1988. Binding characteristics of Ah receptors from rats and mice before and after separation from hepatic cytosols. 7-hydroxyellipticine as a competitive antagonist of cytochrome P-450 induction. *Eur. J. Biochem.* 172:585-92.
23. Sloop, T.C., and G.W. Lucier. 1987. Dose-dependent elevation of Ah receptor binding by TCDD in rat liver. *Toxic. Appl. Pharmacol.* 88:329-37.
24. Sweeney, G., D. Basford, B. Rowley, and G. Goddard. 1984. Mechanisms underlying the hepatotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. In *Banbury Report 18: Biological mechanisms of dioxin action*, ed. A. Poland and R.D. Kimbrough. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.
25. Bacher, M.A., and G.G. Gibson. 1988. Chlorophenoxyacid herbicides induce microsomal cytochrome P-450 IVA1 (P-452) in rat liver. *Chem. Biol. Interact.* 65:145-56.
26. Roberts, E.A., K.C. Johnson, C.L. Golas, and A.B. Okey. 1986. Ah receptor mediating induction on cytochrome P-1-450 detection in human liver by binding of tritiated 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Hepatology* 6:1666.
27. Al-Turk, W.A., M.A. Shara, H. Mohammadpour, and S.J. Stohs. 1988. Dietary iron and 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced alterations in hepatic lipid peroxidation glutathione content and body weight. *Drug Chem. Toxicol.* 11:55-70.
28. Al-Bayti, Z.A.F., and S.J. Stohs. 1987. The role of iron in 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced lipid peroxidation by rat liver microsomes. *Toxicol. Lett.* 38:115-21.
29. Shara, M.A., and S.J. Stohs. 1987. Biochemical and toxicological effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) congeners in female rats. *Arch. Environ. Contam. Toxicol.* 16:599-606.
30. Kohli, K.K., and J.A. Goldstein. 1981. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on hepatic and renal prostaglandin synthetase. *Life Sci.* 19:299-305.

31. Lakshman, M.R., S.J. Chirtel, L.L. Chambers, and P.J. Coutlakis. 1989. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on lipid synthesis and lipogenic enzymes in the rat. *J. Pharmacol. Exp. Ther.* 248:62-66.
32. Tomaszewski, K.E., C.A. Montgomery, and R.L. Melnick. 1988. Modulation of 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity in F344 rats by DI-2-ethylhexylphthalate. *Chem-Biol. Interact.* 65:205-22.
33. Martin, J.V. 1984. Lipid abnormalities in workers exposed to dioxin. *Br. J. Ind. Med.* 41:254-56.
34. Lakshman, M.R., B.S. Campbell, S.J. Chirtel, and N. Ekarohita. 1988. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on de-novo fatty acid and cholesterol synthesis in the rat. *Lipids* 23:904-906.
35. Cantoni, L., A. Graziani, M. Rizzardini, and M.C. Saletti. 1986. Porphyrinogenic effect of hexachlorobenzene and 2,3,7,8-tetrachlorodibenzo-para-dioxin: Is an inhibitor involved in uroporphyrinogen decarboxylase inactivation? IARC Sci. Publ. No. 77:449-56.
36. Goldstein, J.A., P. Hickman, and D.L. Jue. 1974. Experimental hepatic porphyria induced by polychlorinated biphenyls. *Toxicol. App. Pharmacol.* 27:437.
37. Sassa, S., H. De Verneuil, and A. Kappas. 1984. Inhibition of uroporphyrinogen decarboxylase activity in polyhalogenated aromatic hydrocarbon poisoning. In *Banbury Report 18: Biological mechanisms of dioxin action*, ed. A. Poland and R.D. Kimbrough. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.
38. Bleiberg, J., M. Wallen, R. Brodtkin, and I.L. Applebaum. 1964. Industrially acquired porphyria. *Arch. Dermatol.* 89:793-97.
39. Jirasek, L., J. Kalensky, K. Kubec, J. Pazderova, and E. Lukas. 1974. In Part 2, Acne chlorina, porphyria cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides. *Czech Dermatol.* 49:145-57.
40. Lucier, G.W., R.C. Rumbaugh, Z. McCoy, R. Hass, D. Harvan, and P. Albro. 1986. Ingestion of soil contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters hepatic enzyme activities in rats. *Fundam. Appl. Toxicol.* 6:364-71.
41. Ideo, G., G. Bellati, A. Bellobuono, A. Mocarelli, P. Marocchi, A. and P. Brambilla. 1982. Increased urinary d-glucaric acid excretion by children living in an area polluted with tetrachlorodibenzodioxin (TCDD). *Clin. Chem. Acta.* 120:273-83.
42. Ideo, G., G. Bellati, A. Bellobuono, and L. Bisanti. 1985. Urinary d-glucaric acid excretion in the Seveso area, polluted by tetrachlorodibenzo-p-dioxin (TCDD): Five years of experience. *Environ. Health Perspect.* 60:151-57.
43. U.S. Centers for Disease Control. Health status of Vietnam veterans. In Part 2, Physical health. The Centers for Disease Control Vietnam experience study. *JAMA* 259:2708-14.
44. Oliver, R.M. 1975. Toxic effects of 2,3,7,8-tetrachlorodibenzo 1,4-dioxin in laboratory workers. *Br. J. Ind. Med.* 32:49-53.
45. Reggiani, G. 1980. Acute human exposure to TCDD in Seveso, Italy. *J. Toxicol. Environ. Health* 6:27-43.

46. May, G. 1973. Chloracne from the accidental production of tetrachlorodibenzodioxin. *Br. J. Ind. Med.* 30:276-83.
47. Suskind, R.R., and V.S. Hertzberg. 1984. Human health effects of 2,4,5-T and its toxic contaminants. *JAMA* 251:2372-80.
48. Oliver, R.M. 1975. Toxic effects of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin in laboratory workers. *Br. J. Ind. Med.* 32:46-53.
49. May, G. 1982. Tetrachlorodibenzodioxin: A survey of subjects ten years after exposure. *Br. J. Ind. Med.* 39:128-35.
50. Moses, M., R. Lilis, K.D. Crow, J. Thornton, A. Fischbein, H.A. Anderson, and I.J. Selikoff. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: Comparison of findings with and without chloracne. *Am. J. Ind. Med.* 5:161-82.
51. Hoffman, R.E., P.A. Stehr-Green, K.B. Webb, G. Evans, A.P. Knutsen, W.F. Schramm, J.L. Staake, B.B. Gibson, and K.K. Steinberg. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *JAMA* 255:2031-38.
52. Assennato, G., P. Cannatelli, and I. Ghezzi. 1986. Health surveillance of a potential TCDD-exposed industrial population in Seveso: Pattern of some liver-related biochemical indicators. In *Occupational and environmental chemical hazards: Cellular and biochemical indices for monitoring toxicity*, ed. V. Foa, E.A. Emmett, M. Maroni, and A. Colombi. Chichester, England: Ellis Horwood Limited.
53. Mocarelli, P., A. Marocchi, P. Brambilla, P. Gerthoux, D.S. Young, and N. Mantel. 1986. Clinical laboratory manifestations of exposure to dioxin in children. *JAMA* 256:2687-95.
54. Webb, K.B., R.G. Evans, A.P. Knutsen, S.T. Roodman, D.W. Roberts, W.F. Schramm, B.B. Gibson, J.S. Andrews, Jr., L.L. Needham, and D.G. Patterson. 1989. Medical evaluation of subjects with known body levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J. Tox. Environ. Health* 28:183-93.
55. Thomas, W.F., W.D. Grubbs, T.G. Karrison, M.B. Lustik, R.H. Roegner, D.E. Williams, W.H. Wolfe, J.E. Michalek, J.C. Miner, and R.W. Ogershok. 1990. Epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: 1987 followup examination results, NTIS: AD A 222 573. USAF School of Aerospace Medicine, Human Systems Division, Brooks Air Force Base, Texas.